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SPEECHES, ARTICLES, AND SELECTED PAPERS

By

James B. Wyngaarden, M.D.

1982-1988

Volume 4 (of 5)

(December 8, 1986—November 12, 1987)

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Speeches, Articles, and Selected Papers
James B. Wyngaarden, M.D.

1982-1988
Volume 4

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REMARKS*

BY

JAMES B. WYNGAARDEN, M.D.**

FRIENDS' BIRTHDAY PARTIES ARE USUALLY VERY PLEASANT OCCASIONS, AND I BELIEVE THIS ONE HAS AN ADDED ATTRACTION AS A SORT OF DUAL OBSERVANCE. THE SERVICES THE DIVISION OF RESEARCH SERVICES PROVIDES TO OUR INTRAMURAL INVESTIGATORS ARE ESSENTIAL TO THE BIOMEDICAL RESEARCH EFFORT, SO NATURALLY THEY WERE NEEDED AND SUPPLIED LONG BEFORE DRS WAS ORGANIZED 30 YEARS AGO. THE SCIENTISTS OF THE HYGIENIC LABORATORY, LATER THE NATIONAL INSTITUTE OF HEALTH, AND ULTIMATELY THE NATIONAL INSTITUTES OF HEALTH, THROUGH ONE ORGANIZATIONAL STRUCTURE OR ANOTHER, HAD LIBRARY SERVICES, LABORATORY ANIMAL SUPPORT SERVICES, BIOMEDICAL ENGINEERING AND INSTRUMENTATION SERVICES, AND MEDICAL ARTS AND PHOTOGRAPHY SERVICES. ADMITTEDLY THE SERVICES WERE MUCH SIMPLER THAN THOSE REQUIRED FOR TODAY'S RESEARCH BUT THEY WERE AS MUCH A PART OF RESEARCH THEN AS NOW. SO THIS GATHERING IS NOT MERELY THE 30TH ANNIVERSARY OF DRS, BUT AN INTEGRAL PART OF THE NIH CENTENNIAL-- A RECOGNITION OF SOLID AND LONG-STANDING CONTRIBUTIONS TO NIH RESEARCH.

THE IMPETUS FOR CREATING DRS IN 1956 WAS THE RAPIDLY INCREASING SIZE AND COMPLEXITY OF RESEARCH SUPPORT NEEDS IN THAT PERIOD OF EXPONENTIAL GROWTH FOR NIH. CONTINUING GROWTH AFTER 1956 LED TO THE ELEVATION OF THREE DRS BRANCHES INTO SEPARATE DIVISIONS: COMPUTER RESEARCH AND TECHNOLOGY, ENGINEERING SERVICES, AND SAFETY. AS NIH HAS RESPONDED ORGANIZATIONALLY TO NEW NEEDS AND NEW OPPORTUNITIES, SO DRS AND ITS FOUR BRANCHES HAVE ADAPTED THEMSELVES TO NEW NEEDS OF THEIR INTRAMURAL SCIENTIST "CUSTOMER," AND THEY HAVE ALSO OFFERED THOSE SCIENTISTS NEW AND UNEXPECTED TOOLS.

IT IS HARD TO IMAGINE AN NIH LIBRARY WITH NO COMPUTERIZED BIBLIOGRAPHIC SEARCHES, A VETERINARY RESOURCES BRANCH WITH NO GERM-FREE ANIMALS, A BIOMEDICAL ENGINEERING AND INSTRUMENTATION BRANCH WITH NO EXPERTISE IN

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*PRESENTED AT THE DIVISION OF RESEARCH SERVICES CELEBRATION OF THEIR 30TH ANNIVERSARY AND THE NIH CENTENNIAL, DECEMBER 8, 1986.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

ELECTRONICS OR IMAGING TECHNIQUES, A MEDICAL ARTS AND PHOTOGRAPHY BRANCH WHERE NO ONE EVER HEARD OF A "POSTER SESSION", BUT THAT WAS THE NIH AND THE DRS OF 30 YEARS AGO. MANY OTHER AND WIDELY DIFFERENT EXAMPLES OF PROGRESS COULD ALSO BE CITED.

IT IS A GREAT PLEASURE TO BE PRESENT AS THE MEN AND WOMEN OF DRS MARK THE 30TH ANNIVERSARY OF YOUR DIVISION'S EFFORTS TO MEET NIH RESEARCH SUPPORT NEEDS IN YOUR AREAS OF EXPERTISE. IT'S AN EVEN GREATER PLEASURE TO BE ABLE TO SAY, IN THE NAME OF OUR INTRAMURAL INVESTIGATORS PAST AND PRESENT, "THANK YOU".

OPENING REMARKS*

by

James B. Wyngaarden, M.D.**

I am pleased to be with the Interagency Human Subjects Coordinating Committee and other department and agency representatives today, as you consider the important work ahead to implement the Model Federal Policy. I join you today to congratulate you and to support the Office for Protection from Research Risks (OPRR) in its coordinating tasks that have accelerated in the last few months as the Final Model Federal Policy is nearing publication.

Concern about protecting human subjects in research is not new to us at NIH. Thirty years ago when the Clinical Center opened, NIH instituted the first Federal policy requiring prospective independent ethical review of all research proposing to involve human research subjects under Clinical Center auspices.

In the early sixties, the NIH Director, Dr. James Shannon, recognized the need for NIH to be the pacesetter in establishing ethical standards for clinical research. Dr. Shannon took the leadership in developing a set of ethical standards that were intended to be every bit as exacting in protecting research subjects as NIH's scientific standards were in protecting the integrity of research. He commissioned a study in 1962 at the Boston University Center for Law and Medicine to examine possible measures to assure adequate protections for human research subjects. Then, after further review and recommendations by a blue ribbon panel of NIH researchers, Dr. Shannon proceeded to win endorsement of the proposed measures as the policy for the entire Public Health Service (PHS). The PHS adopted it as policy in 1966.

The basic features of the 1966 PHS Policy and the accountabilities enumerated remain today and are now a part of the Model Federal Policy. The Department of Health and Human Services since 1974 has had regulations based on these features. They have been endorsed and adopted throughout the world, by the World Health Organization and the Council of International Organizations of the Medical Sciences. Two Congressionally-mandated commissions have studied and favorably reported on them, and they have been reviewed and discussed in scholarly circles and public forums for nearly two decades. These subsequent initiatives and the thoughtful comments of critics and supporters have enriched the basic features set out by the original NIH proposal. But the fundamental soundness and workability of the 1966 PHS Policy have been reaffirmed repeatedly and public agencies and private institutions have adopted it widely to ensure the protection of individuals who participate as subjects of research.

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*Presented at the Interagency Human Subjects Coordinating Committee Workshop, Linden Hill Hotel, Bethesda, on December 9, 1986.

**Director, National Institutes of Health, Bethesda, Maryland.

A basic principle that has been articulated throughout the many phases of development of the Model Federal Policy is the fostering of advances in research while minimizing the risk and distress to research subjects and ensuring their willing and enlightened cooperation. You are in a key position to articulate this principle in your deliberations on implementation of the Model Policy.

One aim of the Model Policy is to ensure that all those involved in research think about their responsibilities. It offers a guide to be followed, a structure that assists us in analyzing the complex ethical problems that may occur in the course of research.

The Policy both encourages and focuses careful thinking about the rights and welfare of human subjects. This consideration takes place on three levels --the level of principle, the level of procedure, and the level of activity.

1. On the level of principle--The Belmont Report, about which you will hear more later this morning, enunciated three principles that ought to guide research involving human subjects:

   A. Respect for persons--which calls for us to hold the autonomy of the individual in highest regard;

   B. The principle of beneficence--which calls for us always to minimize the possibility of harm and never to authorize research which is not intended to benefit individuals or society; and

   C. Justice--which calls for us to distribute fairly among all groups the risks and benefits of research.

2. On the level of procedure--The assessment takes place in the review at the institution by the Institutional Review Board (IRB). Here at NIH, additional review of proposed activities to identify any possible hazards or unwarranted risks, takes place in our scientific peer review groups--the study sections--and by our National Advisory Councils. Program staff and the Office for Protection from Research Risks constitute two more levels of review here at NIH. All this enables us to reassure those to whom we remain accountable--the public and the Congress--that every precaution is taken to ensure that safeguards are adequate.

3. On the level of activity--Program, contracts, and grants management staff at the NIH level review reports on the research to make sure that the research continues to follow the approved research design. At the institution, the IRB and the officials of the institution maintain contact with the researchers in appropriate ways at proper intervals, depending on the degree of risk, to see that no problems occur. But it is at the point of the researcher's interaction with the subject that the regulations reach their "moment of truth." Here the reasonableness of well-formulated regulations must provide both instruction and incentive to the researchers.

Your efforts to formulate the final Model Federal Policy have been at the level of Principle. The challenge now is at the levels of Procedure and Activities. In addition to enhancing and extending human research subject protections, we have the opportunity to design Federal procedures with

sufficient uniformity to minimize burdens on the institutions that are our partners in the research enterprise. It is clear that, if the Policy is to succeed, there must be a cooperative relationship among researchers, institutional officials, IRB members, and Federal officials.

Many of you have already moved ahead to incorporate some of the basic elements of the Model Federal Policy into your current operations. Now come a series of key decisions that will make the difference in how well the Policy works. As all bureaucrats know policy can be formulated and regulations promulgated; but the expertise, directives, procedures, documents, administrative systems, and horizontal, vertical, internal, and external communications will determine the success or failure of an endeavor of this scope. I urge you to call upon OPRR to advise you in devising the ways to adapt the implementation efforts to your own organizational settings while maintaining as much uniformity as possible.

In the immediate future, all will need to find internal resources--people, space, dollars, and brainpower--to give this effort some priority. Which will be the offices in your Department or Agency to put the Policy in place, and then to make it work? Will decisions and reviews be done in a central or decentralized way? How will you address human subjects research performed by your own employees versus that supported by grantees or contractors? How will you inform everyone in your organization who needs to know about the implementation efforts? How will you inform those outside your organization who need to know? And, how can you use the experiences of the others here today in developing your plans for implementation?

As you know, OPRR is a coordinating office and, as such, is not charged with approving or disapproving Department or Agency plans. Rather to succeed in this effort, we all must count in large part on the continued mutual goodwill and accountability of the participants and our joint dedication to the worthwhile task at hand to protect human research subjects. Effective communications and borrowing of ideas among all of the members of the Committee will, in large measure, determine the degree of our success in putting the Policy into effective practice. This workshop today is a good example of how to help make this happen.

I wish you well in a time when the diversity of human subjects research is indeed vast. We are pressed for balanced and effective means to perform research that will help us: understand the biological and behavioral mechanisms of AIDS, define genetic codes, match new technology and machinery to human needs, explore space, protect consumers, improve nutrition, prevent mental disabilities and dementias, and better educate our young people. In these and numerous other areas of study, appropriate and ethical human subjects research will be <u>essential</u>. With your help and diligence, this will be possible.

REMARKS*

by

James B. Wyngaarden, M.D.**

On October 16 this year we held official Opening Ceremonies for a year-long observance of the 100th Birthday of the National Institutes of Health. The central theme of the many planned events will be to recall the progress of "A Century of Science for Health," and to look forward to the promise of the second hundred years.

We hope to identify during this centennial year a number of individuals and institutions who have made major contributions to the public health. It is for that reason we are in Framingham tonight.

Not everyone understands that the major portion of the NIH's annual budget is used to support research at medical centers and institutions throughout the country. This is generally referred to as our extramural program and it has been instrumental in supporting work leading to many scientific advances that have greatly enhanced medicine's ability to prevent, treat, or cure disease.

Our intramural program takes place in NIH's hundreds of research laboratories and in our 540 bed research hospital located in Bethesda, Maryland, and staffed by NIH employees. It is generally regarded as one of the foremost biomedical research centers in the world.

It certainly has come a long way from its beginnings. A hundred years ago the National Institutes of Health was a one-room facility in the marine health service hospital on Staten Island. It was called the Hygienic Laboratory and had a sole researcher--Dr. Joseph Kinyoun--a physician and bacteriologist who had at one time worked in the labs of Koch and Pasteur in Europe.

And then, in more recent years, we saw the beginning of the Framingham Heart Study. This program is part of one of our major institutes--the National Heart, Lung, and Blood Institute. It is organizationally located in the extramural program but it has come to symbolize all the major characteristics of the NIH. It is intramural in that the scientists who are responsible for directing the program are NIH employees. It is extramural in that many of the activities of Framingham are carried out in collaboration with major medical institutions that receive support from the NIH. It involves community and reflects the type of partnership that has served and supported NIH well throughout the years. And it also has had the very direct and active involvement of thousands of citizens whom we honor tonight.

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*Presented at the NHLBI Tribute to the Citizens of Framingham, Massachusetts, on December 17, 1986.

**Director, National Institutes of Health, Bethesda, Maryland.

Other speakers will address the notable contributions Framingham has made to the prevention and treatment of cardiovascular diseases.

I would like to simply say thank you to the citizens of Framingham who have made this important study possible. Of all the activities and events that will take place as part of the NIH Centennial, none will better illustrate the good that can come from an active collaboration among scientists, practitioners, patients, and the public than the Framingham Heart Study. Again thank you and congratulations for the splendid contributions you have made during the past 40 years.

REMARKS*

by

James B. Wyngaarden, M.D.**

Even as the Nation has its Founding Fathers, the modern NIH has its "founding family," and we are assembled today to thank that family and to honor Luke and Helen Wilson in particular.

It is true, as we are all aware, that the NIH began in 1887 as a one-room laboratory. But it was here in Bethesda, some fifty years later, that the NIH truly took root and began to grow.

It is difficult to know what would have become of this agency if the Wilsons had never made the generous offer of "Tree Tops" to President Roosevelt. The NIH had been located since 1904 at 25th and E Streets on a five-acre site in two buildings. (Incidentally, those buildings are now occupied by the CIA.) In spite of some interest in locating animal housing facilities out in Beltsville, it is very likely that we would have remained there in the District, severely limited by the size of the grounds and facilities.

In 1935 Mr. Luke Wilson wrote to the Secretary of the Interior offering part of his Bethesda estate to the government, provided a use could be found for it was of some general benefit to the people of the United States. That letter, perhaps fortunately, went unanswered. With characteristic vigor and determination, Mr. Wilson "took it to the top" and wrote directly to President Roosevelt, making the same offer.

President Roosevelt circulated this letter to various government departments. The first, in order of protocol, was the State Department. State was not interested. Then it went to the Treasury. The NIH was actually a part of the Treasury Department for over fifty years, perhaps because, as John Dillinger put it, "that's where the money is."

It was known that we were looking for animal housing facilities, so the letter was referred to then Surgeon General Hugh Cumming. Other government departments also showed interest, and the decision went back to President Roosevelt. Apparently he was something of a Biblical scholar and he knew that "Bethesda" was the healing pool outside of Jerusalem mentioned in John, Chapter 5. The concept of doing health research at the "healing pool" appealed to him. We shall never know how much we owe to the fact that the Bethesda Baptist Church was founded in 1820 on a hill near "Tree Tops."

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*On the occasion of the Dedication of the Wilson Portraits, Wilson Hall, on December 18, 1986.

**Director, National Institutes of Health, Bethesda, Maryland.

The President was also about to appoint a new Surgeon General, Thomas Parran. Dr. Parran saw the Bethesda gift as a future site for the agency. In turn, Dr. Lewis Thompson, soon to be named as the new Director of the NIH by Dr. Parran, had become a close friend of the Wilson family.

I would like to read the letter that President Roosevelt wrote to Mr. Wilson. It captures the moment far better than any commentary.

(READ ATTACHED LETTER)

Later, in 1940, when he dedicated the original buildings of this "campus" President Roosevelt publicly thanked the Wilsons from the steps of this building. Let's listen to a tape of that statement.

TAPED STATEMENT:

> For the very beautiful and very spacious grounds on which these buildings stand we are indebted to Mr. and Mrs. Luke Wilson, who wrote to me in 1935 asking if a part of their estate at Bethesda in Maryland could be used to the benefit of the people of this nation. I would tell her now as she sits beside me that in the compassion of Mr. and Mrs. Wilson for suffering, in their hope for human action to alleviate it, she and her husband symbolized the aspirations of millions of Americans for a cause such as this. And we are very grateful.

Today we make our own gesture of appreciation in the placing of these portraits in "Wilson Hall." I am sorry that Mr. Gonzales, the artist, who is still teaching at Columbia, was not able to be here for this dedication.

It seems particularly appropriate that we do this at Christmas time, because "Tree Tops" was the best present that the NIH ever received. This room is the most pleasant meeting place on the campus and a wide variety of visitors from all over the world come here for symposia that consider every aspect of health and disease. Now they will know why it is called <u>Wilson</u> Hall, in honor of the "founding family" of the modern NIH.

On behalf of the NIH, to all the members of the family assembled here, and to Mrs. Ruth Wilson in particular, let me say thank you. Your generosity will always be remembered.

THE WHITE HOUSE
WASHINGTON

August 19, 1935

My dear Mr. Wilson:

On behalf of the United States Government, may I express my appreciation for the fine gift you have made to the Government for a site for the National Institute of Health of the Public Health Service.

The question which you raise as to the continued use of the land by the Public Health Service seems to me to be answered by reference to the stability of that Service and the National Institute of Health in the past.

The National Institute of Health which you refer to in your letter was established in 1887 for the investigation of contagious and infectious diseases. After forty-eight years, this institution still remains the center of medical and public health research of the Government. It is true that its functions have changed in the passage of years because of the changing needs of the Government, but such changes have added to its prestige and stability and have not detracted from them.

Finally, the Social Security Act, which I have just signed, makes public health research an integral part of a great program looking toward the social security of the nation.

May I again express my appreciation not only of the gift which you have made to the people of this country but also of the high purpose for which it was given.

Very sincerely yours,

Franklin D. Roosevelt

Luke I. Wilson, Esq.,
Bethesda, Maryland

CENTENNIAL THOUGHTS ON BIOMEDICAL RESEARCH*

by

James B. Wyngaarden, M.D.**

The National Institutes of Health is now in its one hundredth year. Observance of the centennial began last October and will continue through October of this year with a variety of ceremonies and events held in many different places in the United States and overseas. While the focus will be on the story of the remarkable growth of NIH, the history of the blossoming of the biological sciences in the past century, particularly in the latter half, will occupy a central place in our observances. In the course of my remarks, I will recount some of the chapters of the NIH history. But as interesting as the past may be to those of us who are now a part of the agency, I find my centennial thoughts more concerned with the promising future, not only of the NIH but also of biomedical research as such.

In visiting an institution of higher learning, and especially in meeting and talking with young physicians to-be and with scientists in training, I find myself envious of the highly interesting opportunities they will have to participate in great leaps in understanding. These seem almost certain of realization during the professional career of many of today's students.

We truly are in a period of extraordinary accomplishment and advance. Old problems are yielding to new tools at an increasingly rapid rate. Even more basic to this rapid progress is the store of biomedical knowledge that has been amassed in recent years. This has made possible tremendous advances in the improvement of human health.

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*Distinguished Lecture presented at University of New Mexico, Albuquerque, January 12, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

The biological revolution is far from over and, in fact, is now approaching major questions with immediate relevance to the practice of medicine. Key discoveries in molecular biology, genetics, and immunology have led to the widespread use of techniques that are enabling scientists to address fundamental questions about the nature of living organisms.

Cells and bacteria can be transformed into factories to produce custom-made monoclonal antibodies or valuable hormones and growth factors. These advances, many of which were made in the past decade, are still diffusing into existing fields of investigation. Questions that went unanswered for lack of appropriate technology are now under attack. Their solutions will accelerate our progress against disease as well as raise new questions to explore.

I will mention, as examples, a few accomplishments that promise to lead to opportunities for new achievements in diagnosis, treatment, prevention, and understanding of the processes underlying disease states.

One area of current progress and promise is structural biology. Work on cell membrane and receptor structure and function may lead to design of tailor-made drugs for more effective tailor-made action. Recently, investigators have determined the complete, three-dimensional architecture of a common cold virus using x-ray crystallography employing a high energy synchrotron source and area scanners. Scientists have long known the general shape of the cold virus, which under the electron microscope shows an outer wall composed of 20 triangles to form the shape of an icosahedron. Inside the hollow protein shell is the genetic material which, when released, directs the cell to replicate the virus.

The new studies provide a stereo view of the position of the molecules making up the protein structure showing that each triangle of the protein shell has peaks and valleys formed by the irregular shape of protein molecules making up the shell. The part of the shell that must attach to a cell to cause infection lies within a deep cleft or "canyon" on each of the 20 triangular sides and appears to be too narrow for antibodies to reach. This finding, however, raises the possibility that a molecule could be

synthesized that would be small enough to enter the canyon and bind to the attachment site, preventing attachment of the virus to the cell, and consequently preventing infection.

This insight has significance far beyond its application to prevention of the common cold. The whole roster of viral-caused disease, including AIDS, may be vulnerable to this strategy.

Technological advances in such areas as x-ray crystallography and magnetic resonance imaging have provided such new opportunities to investigate the structural properties of physiologically active molecules. One of the most revealing and rapidly evolving research tools now being used by molecular biologists is magnetic resonance imaging spectroscopy. With this technique it is possible to determine the chemical composition of biologically important molecules, the length and nature of the bonds holding the atoms of the molecule together, and the three-dimensional arrangement of those atoms. A significant advantage of this technique is that studies can now be performed on molecules in their typical physiologically active state, that is, either within the living organism or in aqueous solution rather than in an unnatural solid state.

Better understanding of structural biology is but one example of the areas of knowledge where progress and promise are substantial and exciting.

The 1880s were also a time of ferment and rapid advancement in biology in chemistry and in physics. It is interesting to note how many scientific institutions, societies and other organizations in this country and abroad are celebrating their 100th anniversary in this decade. But in biomedicine most of the action was overseas.

The NIH came into being at a time when medical science in the United States lagged far behind the state of knowledge in Europe. Fruitful studies in the new discipline--bacteriology--led by Robert Koch and Louis Pasteur--were taking place in many European laboratories but few Americans had participated in those advances. The yellow fever epidemic of 1878 had created widespread alarm in the United States and a variety of measures

were proposed for its prevention and control, none particularly effective. Other communicable diseases, such as cholera and tuberculosis, were also matters of serious concern. Because travelers and immigrants were thought to be bringing the diseases into the country, efforts to arrest this spread of contagion were concentrated at ports of entry. Thus, in 1887 a one-room laboratory was set aside in the Marine Hospital on Staten Island in the Port of New York dedicated to research on communicable diseases. Called the National Laboratory of Hygiene, this modest facility ultimately became the National Institutes of Health. The laboratory was a fragile transplant from European medical science.

Soon after establishing the hygienic laboratory, its director Dr. Joseph J. Kinyoun arranged for a six-month assignment to two of the most famous laboratories in Europe, that of Dr. Robert Koch in Berlin and the laboratory founded by Louis Pasteur in Paris. The Pasteur Institute, by the way, is one of the centenarians to be celebrating a birthday in 1987. The NIH and the Pasteur Institute will hold a joint 100th birthday seminar at our headquarters in Bethesda in late May.

For the first 50 years of its history, the National Institutes of Health was essentially an independent, free-standing laboratory of limited size but of substantial accomplishment. It was moved to Washington well before the turn of the century and engaged some of the most serious public health problems of the time.

A giant among the remarkable members of the staff was Dr. Joseph Goldberger. As one of the most promising young men connected with the Laboratory, he was placed in charge of the investigation of pellagra, then prevalent in the poverty-stricken South but a problem in 40 states as well as the District of Columbia. Pellagra was thought by most medical scientists of the time to be caused by a particular organism, and the search for it was on. Dr. Goldberger argued that if a bacillus were the cause, some of the doctors, nurses, and other attendants working around pellagra patients would get it too. He noted that the one difference between the inmates in prisons and mental institutions and the people who cared for them was their diet--yet many of the inmates suffered from pellagra and their attendants did not. Dr. Goldberger showed that the poor

diets common to many low-income people--diets high in carbohydrate and low in good quality protein and fresh vegetables--induced pellagra when fed to volunteer convicts in a Mississippi penitentiary. In other public institutions where the disease occurred he and his associates demonstrated that generous amounts of milk, eggs, meat, beans and peas prevented it. Still, physicians who were treating pellagra strongly believed that it was due to an infectious organism and would not accept Goldberger's evidence.

As a final proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later, Goldberger and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous patient into his wife Mary. None contracted the disease, though it is not recorded what adverse symptoms may have resulted from these heroic experiments.

He later developed a treatment using yeast in the diet and showed that the amino acid tryptophan was crucially related to the cause of the disease. Soon the B vitamin nicotinic acid, now called niacin, was identified as a specific pellagra preventive.

The modern era of the NIH, as well as that of biomedical research in our country, began when the Government and non-Government research laboratories, mostly in academic institutions, joined their efforts in carrying out research during World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the armed services, the Government turned to the established, non-Federal laboratories for help in conducting vitally important research. Grants and contracts were awarded for the support of such investigations. The arrangement worked exceedingly well. The newly-formed partnerships greatly accelerated progress in research and development across the spectrum, from the most basic research to studies on the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

By the end of the War, the U.S. Office of Scientific Research and Development was administering a large number of medically related research projects. A leading American scientist Dr. Vannevar Bush, the President's Science Advisor, urged that the Government continue to support in peacetime the medical research then underway in many universities and hospitals. After Dr. Bush's proposal was accepted, the National Institutes of Health was given the responsibility to administer the ongoing medically related projects. This peacetime collaborative effort marked a significant change in national policy--it was frank recognition of the mutual benefits to be realized from such a partnership.

Dr. Bush's formal recommendations were made in a report written in 1945, titled "Science---The Endless Frontier," He asserted that, "The publicly and privately supported colleges, universities and research institutes are centers of basic research. They are wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth, wherever it may lead, there will be a flow of new scientific knowledge."[1]

Dr. Bush was careful, however, to emphasize that in the course of supporting research and training, the Federal Government should not interfere with the freedom and integrity of academic institutions. Specifically, he recommended that Government grants should allow complete independence and freedom for the scientists to determine the nature, scope, and methodology of his or her investigations. "Scientific progress," he said, "results from the free play of free intellects working on subjects of their own choice in the manner dictated by their curiosity for exploration of the unknown."[1] It is on this philosophical foundation that the research programs of the National Institutes of Health were established and continue to flourish.

Our commitment to fundamental research has been sustained over the years, in fact, it has grown stronger. In 1970 it was estimated that 30 to 35 percent of our budget was for basic research. By 1980 basic research was 52 percent. In 1986 it was increased to 63 percent. This rapid

increase is partly due to the priority we have given to investigator-initiated grants and partly to a marked decline in our use of contracts. It also reflects the accelerated pace of discovery in molecular biology, genetics and other exciting areas.

The key instrument that NIH has used to provide support for biomedical research is the project grant. Each such grant is made to fund an investigator-initiated project proposed to NIH by an individual scientist. In 1986 more than 57 percent of the total NIH budget was devoted to investigator-initiated project grants. We believe that they foster creativity and excellence and are an effective instrument for involving our Nation's finest scientists in the national effort to improve health through the advancement of knowledge.

A turning point in the history of the NIH took place in a short period of five years from 1940 to 1945 when the NIH changed from a small Federal laboratory, whose activities were almost entirely in-house, to an agency whose focus turned increasingly to the support of research in non-Federal institutions. Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that have been spectacular. In terms of purchasing power in constant dollars the total budget of NIH grew from 1945 to 1968 at an astounding average rate of 24 percent per year. The growth rate from 1968 to 1982, taking inflation into account, was about 2 percent per year. Beginning about four years ago, there has been a steady growth so that the 1987 budget exceeded the 1982 total by $2.5 billion, or 70 percent in current dollars.

The extremely rapid expansion of the NIH budget in the earlier period resulted in part from extension of the scope of the agency through the creation one-by-one of new institutes. There are now 12 institutes, most of them oriented to specific organ systems or to families of diseases, as for example the National Heart, Lung, and Blood Institute, the National Eye Institute, the National Cancer Institute, and the newest--the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

It was inevitable that the steep climb in the NIH budget must taper off and it began to do so in the mid 1960s. To forestall, or at least to

ameliorate this change, dedicated proponents of biomedical research took the offensive first under the banner of initiatives against the killers--heart disease, cancer and stroke, and a few years later under the flag of a war against cancer. For a time in 1971 the Democratic Congress and the Republican Administration attempted to outbid each other in terms of appropriations and organizational innovations to hasten the conquest of cancer. Subsequently proponents of research on heart disease also were successful in attracting special attention and funds for research with this number one killer.

In the early 1970s there was a remarkable revision of national priorities toward cancer, heart disease, and to a lesser extent, stroke. By the late 1970s, however, the growth differentials between institutes had largely evened out. While the momentum of ongoing programs has been maintained, new areas of priority--for example AIDS--are receiving necessary attention. Other priority areas are beginning to become clearly discernable as the result of progressive increases in understanding.

An example of how new understandings open the door to yet more quests for understanding has received much attention within the scientific community of late. Molecular biology has progressed to the point where it is now possible to characterize the human genome by obtaining complete nucleotide sequences of its three billion components.

Some aspects of the current situation bring to mind the discussions and consideration that involved much of the biosciences community some twelve years ago when the recombinant DNA technique became widely known. The climate differs in one major way, however, from that which prevailed in the early days of recombinant DNA research. Then there was concern about proceeding because of the possibility of unknown environmental hazards. Characterizing the human genome poses no such risks, but doubts have been expressed about the wisdom of committing the enormous resources that would be required for an all-out accelerated program. Former NIH Director Donald S. Fredrickson, comparing the current opportunity with that presented by recombinant DNA said, "We now face a new challenge, this time more awesome than dangerous."

Several important conferences of leading scientists have been held during the past twelve months for the purpose of assessing the feasibility of mapping and deciphering and analyzing all the messages of all the genes of the human body. One of the first such meetings was held last March when the Department of Energy sponsored a workshop in nearby Santa Fe that was attended by more than 40 scientists from the United States and Europe.

Last fall at a meeting of the NIH Director's Advisory Committee four questions were addressed--Why should such a massive project be considered and of what importance is the knowledge gained? Is there a realistic possibility that the project can be accomplished? What is the best way to carry out the task? And what will it cost?

There was full agreement on the potential benefits. This new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and the molecular bases for inherited disease; we would gain substantial new information on neoplastic and malignant disorders as well as on autoimmune and immune deficiency diseases; an extensive new science base would be created of special importance to studies of toxicology and the effects of environmental contaminants; and the potential for effective gene therapy would be enhanced.

It is clear that the technology exists for completing a major portion, if not all, of the task. There is general confidence that the necessary improvements in methodology will be developed to deal with certain problem areas and thus make possible the total characterization.

The most pressing problem is to devise means for dealing with the vast amount of data that will be generated by the genome project. Databases established to handle DNA sequence information are currently swamped. GenBank, which is the United States' database, was planned and launched by the NIH's National Institute of General Medical Sciences. It is funded as an interagency project involving the Departments of Energy and the National Science Foundation, as well as four components of the National Institutes of Health. GenBank is located just up the road, at the Los Alamos National Laboratory. The European Molecular Biology Laboratory at Heidelberg

established a DNA database in 1980. It has been estimated that both of these bases have grown 25 fold in the short time they have been in operation, but that the genome project would call for the handling and storage of 1000 times as much information as is currently being processed.

It was the consensus at our recent advisory committee meeting that a carefully planned stepwise effort rather than a mass attack is the method of choice. This would call for first mapping of relatively large segments of the genome, then determining the precise sequence of bases in segments of particular interest because they are involved in genetic diseases or bodily processes. This approach would defer, at least for a time, determination of the sequences of the rest of the genome.

If approached in accordance with this suggestion the initial expense would be within reach. It has been estimated that to prepare a macro map of restriction fragments would require about $100 million over a five-year period. This is well within the current NIH budget. Full sequencing would follow and would be within financial feasibility if attention is first directed toward development of more efficient methods for cloning of gene fragments.

While discussing the massive enterprise entailed in mapping the human genome I must mention recent successes in the field of genetic mapping. For instance, the discovery of genetic markers for cystic fibrosis and Huntington's disease. This research and related work opens up the possibility of isolating the gene and the gene product. Then the nature of the genetic defect would become apparent, perhaps permitting the development of more rational treatment or prevention strategies.

Although the marker for cystic fibrosis is diagnostic for most carriers of the disease in families with a history of the disease, it is not specific enough to diagnose asymptomatic carriers in the general population. Such a test requires isolation of the CF gene itself, a task now technically feasible because of the new findings.

Treatment of genetic disease by introduction of normal genes into the cells of affected patients is a formiable challenge. Nonetheless, great progress has been made in recent years through efforts in the NIH intramural research program and through extramurally supported research. Much attention has focused on adenosine deaminase (ADA) deficiency, a rare disorder that causes severe defects in immune function leading to infection and death during early childhood. Indeed, ADA may be the first target disease for gene therapy. However, the methods and knowledge acquired in this effort are directly applicable to the treatment of other diseases such as Cooley's anemia.

Where existing strategies have been successful there is every reason to continue their use. But the success of conventional strategies has been limited, and clearly new ones are needed for a range of devastating diseases for which there is at present no ameliorative or curative approach. Thus we come face to face with the topic of human gene transplantation for somatic cell defects, a discussion of candidate conditions, the state of science in the field and ethical issues and public expectations engendered by these prospects.

I cannot leave this subject without noting that application of a strategy for gene therapy in humans will require experience in an animal model where the clinical situation is reproduced realistically. This area of research provides a striking example among the many where there is no substitute for the use of an intact animal model--where promising progress would be halted abruptly if research with animals were to be prohibited. And that is the agenda of at least some of the so-called "animal rights" activists. Their activities increase in spite of all actions by research institutions to improve facilities, oversee research and punish wrongdoers. It is a fallacy to assume that the major goal of these groups is the better treatment of animals. The ultimate objective is nothing short of the abolition of all research involving animals. I daily am more convinced that such attacks on medical science must be taken seriously and that we as researchers and physicians must respond. Whether fueled by ignorance or naivete, cries to outlaw animal experimentation must be countered with scientific fact and reaffirmation of our commitment to improving human

health through responsible use of animals. We are witnessing a resurgance of antivivisectionism which during the past century has emerged and reemerged--though never before has it been so skillfully promoted.

This thought leads me back to my original theme--Centennial thoughts. In examining a 100-year span one inevitably encounters cycles.

In the early part of the twentieth century spectacular achievements in public health resulted from non-therapeutic measures, such as mosquito control and improved nutrition. These measures, however, were taken because researchers had learned the causes of killers such as yellow fever and pellagra. Some thirty years later the pendulum had swung to emphasis on the antibiotics and the continuing search for a "magic bullet." In the past decade, with no dimunition of the search for new therapies, there has been a renewal of interest in the importance of disease prevention by means other than therapeutic agents, through emphasis on behavioral change.

Last month the U.S. Public Health Service issued a progress report on the health of the American people. Among the major findings were the significant and continuing declines in death rates for both heart disease and stroke--that now rank first and fourth among the causes of death in the United States. Between 1972 and 1984 the death rate from heart disease fell 34 percent; since 1980 the rate has fallen by 9 percent. In the same 12-year period, the death rate from stroke fell 48 percent; and since 1980 has fallen 17 percent[2]. These steep drops are credited mostly to changes in such factors as smoking, diet and blood pressure control.

With each swing of the pendulum the resources at hand for improvement of health are augmented. This generation is challenged to use well all of the hard-won measures we have for the prevention of disease and the improvement of health, and to intensify the search for even more effective instrumentalities.

I would be pleased to answer any questions you may have.

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METROPOLITAN LIFE FOUNDATION AWARDS*

by

James B. Wyngaarden, M.D.**

I am delighted to have a part in this program and to speak on behalf of the National Institutes of Health in extending warmest congratulations to the winners of the Metropolitan Life Foundation Awards for Medical Research. I also wish to commend the Foundation for establishing this generous award program that not only recognizes accomplishment but enables further pioneering effort by the awardees. The choice of Alzheimer's diseases for emphasis just now is especially timely.

Alzheimer's disease is one of the most devastating and feared of the many disorders associated with growing older. It has been stated aptly that Alzheimer's disease not only causes a variety of physical, psychological and emotional changes and loss of memory--it also leads to loss of self. The urgency of the problem arises not only from the tragic nature of the disease but also from the fact that it affects a substantial portion of older people. It is estimated that between 2.5 and 3 million people have Alzheimer's disease and that the total cost of their care adds up to nearly $90 billion per year.

Older people face the greatest risk of developing Alzheimer's disease--the older they are, the greater the risk. More than one half of the people who have ever survived to age 65 are alive today--and as many as one of every ten has Alzheimer's disease. A large number of older people alive today will survive to age 85 when their chances of developing Alzheimer's disease may be one in three unless new understanding of this disease through research can point the way to effective treatment, or better still to its prevention.

The Metropolitan Life Foundation performed a valuable service last year in making widely available for the families of Alzheimer's disease victims the film on "Caring," for this disease not only raises complex social and economic issues for society, it also presents enormous problems to patients' families.

The fact that the Foundation only a short time later can sponsor a major award program for research on the disease suggests a significant and rapid change in our perception of Alzheimer's disease. It no longer is regarded simply as a natural consequence of aging. We now know that Alzheimer's disease has a specific pathologic changes in the brain and must have a specific cause.

Today's awards are made for research advances that represent early steps in the kind of understanding that must be gained if we are to develop eventually distinct approaches to prevention and treatment.

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*Address presented at the of Metropolitan Life Foundation Awards Luncheon in New York, New York, on January 19, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

In the broad perspective, the major health problem of our times lies in the continued existence of diseases for which we can do little. The problem is not primarily the cost of the required care or its distribution, inequitable and serious as these problems may be. Even if the best of contemporary medicine were universally available without financial barriers, cancer would continue to kill, rheumatoid arthritis would continue to cripple, and Alzheimer's disease would continue to devastate. Because of a lack of scientific understanding we have no definitive answers to these and many other diseases for which the best we can offer is what Lewis Thomas has called "halfway technologies": measures that may modify but do not prevent or cure.

Medicine as a science is incomplete, just as science by its nature is incomplete. But as today's awards attest, we know more about Alzheimer's disease than we did ten years ago and with such knowledge is established a sense of direction for the search.

Each year the National Institutes of Health is asked to submit to the House Appropriations Committee a set of special reports on the current state of knowlege on some twenty topics as selected by the Committee. Alzheimer's disease has been a topic for the past three years. In reviewing the latest reports prior to their mid-January submission to the Congress, I was pleased to note that both of today's awardees are mentioned, and that their work is cited as evidence of significant progress. The report will take note that a major issue still challenging science is the diagnosis of Alzheimer's disease, and will tell of the work of Dr. Peter Davies and of his findings that point to the possiblity of a chemical test to diagnose Alzheimer's disease. In another part of the report there will be an account of the investigations by Dr. Dennis Selkoe and his colleagues on the tables of unique proteins in the brain and the relationship of these studies to efforts to determine the cause of Alzheimer's disease.

About two years ago, Dr. Caleb Finch of the University of Southern California was quoted in an editorial in Science magazine in which he said: "I would not be surprised if the major new resources required for a serious attack on Alzheimer's disease do not also benefit the basic neurosciences on the same scale as funding for cancer research has done for many areas of molecular, cell, and developmental biology." The fact is that research on Alzheimer's disease is so broad in its reach that it is already having an impact on basic neuroscience and other research; while at the same time, basic neuroscience and other research is shedding new light on Alzheimer's disease.

This, indeed, is a time of exciting progress in the neurosciences. New insights are emerging on the plasticity of the nervous system. Nerve regeneration, once thought to be confined to peripheral nerves is a subject of intense study in the central nervous systems of certain animals. Such investigation has special significance for scientsts seeking means for promoting true recovery of spinal cord-injured patients. One of the most tragic medical problems facing our Nation is spinal cord injury--that, in contrast to Alzheimer's disease,--strikes hardest at youth. About 10,000 spinal cord injuries occur each year in the United States.

The winners of the 1986 Nobel Prize, Dr. Rita Levi-Montalcini and Dr. Stanley Cohen, received the award for their discoveries of growth factors involved in regulating nerve and skin cells. Their work was cited by the Nobel

Committee as opening new fields of widespread importance in basic science, that may increase understanding of numerous disorders including birth defects, cancers, muscular dystrophy, and Alzhemier's disease.

The scientific ferment now evident in the neurosciences is accompanied by progress in a much more mundane but essential area. Some sixty voluntary and professional organizations concerned with neurological and communicative disorders have come under the banner of the National Committee for Research on Neurological and Communicative Disorders, for the purpose of increasing public awareness of the need for research across the spectrum of the many and various disease problems about which they are primarily concerned. The Alzheimer's disease and Related Disorders Association is a member of the coalition. Such joint efforts are bound to have an important effect upon public awareness and in turn upon private and public support for essential research.

The Metropolitan Life Foundation Awards for Medical Research will have the effect also of increasing public awareness, and at the same time offer a powerful incentive to scientists as well. Once again, I offer my warmest congratulations to the awardees and to the Foundation.

REMARKS*

by

James B. Wyngaarden, M.D.**

It is a pleasure to meet with you today. I thought I would begin by noting some of our plans for the celebration of the NIH Centennial and then discuss our goals in strengthening the research environment and providing support for research training and career development. I plan to share with you an overview of the FY '88 NIH budget and I will be pleased to answer any questions you might have on these topics or any others of interest to you.

As you may know, in October the National Institutes of Health began what is to be a year-long observance of its 100th anniversary. During this period there will be centennial seminars, conferences, receptions, dinners, and a variety of events here and in many locations across the United States, and in other countries, providing public recognition of the role of the NIH in what is being described as "A Century of Science for Health." I might note that, as a culmination of this observance, three symposia will be held in connection with a reunion of NIH alumni--those scientists and science administrators who at some time in their careers were researchers or officials at the NIH. I hope that any alunni here today will reserve October 15-18, 1987 to join us for the symposia and reunion.

Another important event in the fall of 1987 will be the broadcast on PBS of a four-part program describing the extraordinary advances that have been made in biomedical research during the past century. The most remarkable of these achievements have occurred in the past couple of decades. While these advances have occurred across the full spectrum of the biomedical sciences, some of the most notable progress has occurred recently in the areas of molecular biology, genetics, immunology, neurobiology, and structural biology.

In addition to the obvious and continuing need to provide adequate financial support for basic research across the full spectrum of the biomedical sciences, there is a growing need to address emerging problems in the research environment. Several recent reports by prominent committees and task forces have drawn attention to the steady and prolonged deterioration that has been occurring in the Nation's research facilities and the growing obsolescence of scientific instruments and major pieces of equipment necessary for the conduct of sophisticated biomedical research.

While the facilities problem is generally adknowledged to be both real and severe, verifiable data regarding the actual state of biomedical research facilities are not available. Consequently, the NIH is participating with the

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*Before the National Advisory Child Health and Human Development Council, January 26, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

NSF in the conduct of a congressionally mandated survey to identify and assess the research facilities needs of universities. When this information becomes available, it will undoubtedly contribute to the dialogue and debate that continues concerning future support of research facilities. In the meantime, as I will discuss later, support for extramural construction will be curtailed.

A recent survey of needs for scientific instruments conducted jointly by the National Academy of Sciences (NAS) and the NIH disclosed that, while there are shortages of instruments and problems with maintenance in a variety of areas, the most significant need is for relatively low-cost pieces of equipment, in the price range of $5,000 to $60,000. In FY '87, Congress provided the NIH $16.0 million to support an instrumentation grant program developed in response to the findings of the survey. Funds are requested in the FY '88 budget to continue support for this program at the same level.

Research Training and Career Development

A prime responsibility remains also to provide a stable research environment and adequate financial support to meet the needs which exist for the training of future investigators. The number of trainees supported by NIH is expected to remain fairly close to the levels recommended by the NAS. However, we are faced with the challenge of determining the optimal deployment of these research training resources to meet a variety of needs. This involves, for instance such questions as:

What should be the mix between predoctoral and postdoctral training?

What is the appropriate balance between individual fellowships and institutional training grants?

What are the special needs and requirements for additional training of M.D.s for careers in research?

Finally, I should note that a research environment in also influenced and shaped by the requirements and conditions imposed by Federal funding agencies such as the NIH. We are keenly aware of the need to constantly review the research grants award system to improve the efficiency and effectiveness of that system. In this regard the NIH has recently introduced award mechanisms designed to provide additional stability for research careers and to increase creativity in the research enterprise.

The Method to Extend Research in Time award provides long-term grant support to investigators whose research competence and productivity are distinctly superior.

The First Independent Research Support and Transition award provides an initial period of research support sufficient for newly independent investigators to establish competence and demonstrate their research productivity.

The Physician Scientist Award provides recently graduated M.D.s extensive research training in both basic and clinical areas to enable them to establish productive research careers.

We continue to work with other Federal agencies and academia to find ways to simplify the research grant award system and foster greater research productivity.

FY 1988 Budget

The FY '88 budget request that was sent to the Congress recently reflects the priority that continues to be placed on the support of investigator-initiated research project grants. It requests support for a total of 19,131 research project grants, 20 more than the FY '87 comparable level. These funds will provide for an average cost of approximately $164,000 per award, the same average cost as the FY '87 comparable level. The request of $233.3 million for research training would support approximately 10,867 trainees, the same number as supported in FY '87, and a level essentially consistent with the recommendations of the NAS. Stipend levels would remain at the FY '85 level.

The $522.0 million requested for research centers represents a decrease of $1.4 million from the FY '87 comparable funding level although these funds will be used to support 560 research centers, the same number as supported in the FY '87 comparable level.

Most of the other NIH research mechanisms--such as research grants, research contracts, research management and support, and disease control--will be maintained at approximately their FY '87 funding levels. Two exceptions are the Biomedical Research Support Grant program and the extramural construction program--both of which are proposed for elimination in FY '88. While both of these programs have definite merit, they are considered of lower priority than the many NIH programs which provide direct support for research and training activities and, consequently, they have been eliminated in the face of budget constraints.

The NIH intramural research program would be increased slightly, about 4.3 percent above FY '87, to provide additional funding for activities related to AIDS research and to absorb mandatory cost increases. The FY '88 budget also includes $20.0 million for continued support of the small and minority universities and colleges program, the same level as in FY '87.

I would be pleased to answer any questions you might have and to hear your views concerning the issues we face in biomedical research.

STATEMENT*

by

James B. Wyngaarden, M.D.**

I applaud the National Library of Medicine for taking the initiative in holding this conference on the Use of Acid-Free Permanent Paper for Biomedical Literature. The problem posed by the deterioration of publications is grave indeed.

This is a matter of special concern to scientists, particularly those engaged in biomedical research. More than many professions the health sciences are dependent upon published literature. Scientist to scientist communication takes place in large part through the two to three thousand leading scholarly journals in which detailed reports of biomedical research are published. It is unusual for a research finding to be reported initially to other than the scientific community through refeered journals or in presentations to peers at scientific meetings. This tradition provides an important safeguard against widespread dissemination of unfounded or premature announcements and helps to avoid wasteful or possibly dangerous use of erroneous information.

Scientific literature has two principal uses. It is a mechanism for communicating new results of research being conducted at this time in laboratories around the world. The knowledge that issues from such laboratories when published is the basis for future discoveries. Scientific literature is a repository of data and information that later is used in laboratories around the world. The knowledge that issues from such may be retrieved and used in ways that had not been considered at the time of the original publication. The recombination of existing data to provide new insights is an important resource for the scientist.

Moreover, today's conscientious medical practitioner must keep pace with the burgeoning store of knowledge, at least as it affects his specialty or practice.

Our system of medical publication, as it has evolved over the centuries, has proved to be an efficient method for distributing information. The assiduous collecting, indexing, and cataloging of the medical literature by the National Library of Medicine is crucial to this effort. More than 100,000 references and abstracts of journal articles and books are added each year to the Library's databases.

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*At the National Library of Medicine hearing on the Use of Acid-Free Permanent Paper for Biomedical Literature, Lister Hill Auditorium, on January 27, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

The innovative methods on online access developed by the Library make this literature quickly and easily available to health professionals and research scientists. The ubiquitous telephone and the rapid proliferation of personal computers ensure that these professionals, no matter how isolated or distant from medical centers their practice may be, now have access to the latest published research advances.

Because medical publishing is so vital to the entire biomedical enterprise--to research, education, and practice--it is important that we address the problem of deteriorating publications. The stakes are high. It is my hope that today's discussions will be a milestone in that effort.

I am encouraged that so influential a man as our next speaker, Representative William Natcher, is here today to give us his perspective. Over the years, Mr. Natcher has given strong and consistent support to both the National Library of Medicine and the National Institutes of Health.

REMARKS*

by

James B. Wyngaarden, M.D.**

I am pleased to meet with you today to discuss the role of the Advisory Committee to the Director, NIH (DAC).

It was established in 1966 in response to a recommendation made in a report to the President on the operations of the NIH by a distinguished committee under the chairmanship of Dean Wooldridge. The Wooldridge Committee noted the needs to be served by such an advisory committee by stating, "In the first place, it will assist the Director of NIH in his important overall planning and policy-determining activities by bringing to bear on the issues involved the highest possible quality of informed and mature judgment. In the second place, the participation of such a non-government group in the major decisions of NIH will provide the needed assurance for the scientific community and the public that the Government is not, through NIH, exerting undesirable influence over the course of health-related science."

While no legislative mandate exists for the DAC, its usefulness has assured its continuation over the last two decades. It provides an advisory apparatus for addressing issues and aspects of NIH activities which, because of their broad and pervasive nature, transcend the program responsibilities of the individual institutes and are more appropriately the subject of trans-NIH concern. Over the years the Committee has contributed to the process leading to the development of a set of research principles to guide the development of national goals and plans for health research; considered the NIH stabilization policy and its effects on the other NIH funding mechanisms; examined issues concerning the costs of biomedical research and the principles governing accountability for federally supported research at universities; discussed the role of NIH in promoting cooperative relationships with industry; served as a public policy forum for consideration of issues concerning the development, promulgation, and revision of the NIH Recombinant DNA Research Guidelines; and explored the policy implications of indirect costs of federally supported research.

I might add, incidentally, that the National Advisory Eye Council, as early as November 1979, developed a resolution which served to call attention to increasing indirect costs and to stimulate debate on policies to address this issue.

Recently we have initiated changes in the format and organization of the DAC to strengthen its role in the NIH policy-formulation process. In the past, each meeting of the Committee addressed a large number and variety of

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*To the National Advisory Eye Council, January 27, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

agenda items with very little time permitted for discussion of the individual topics. In an effort to better focus the deliberations and permit a more in-depth examination of the topics, we decided to limit each meeting to one major subject. This has permitted a much fuller treatment of the issue and, consequently, has increased the effectiveness of the DAC as a deliberative body.

With the change in format, which created a more focused discussion of a single topic, it became necessary to provide greater structure to the deliberations. Accordingly, we now establish a working group to prepare for each DAC meeting. This group--comprised of representatives from the Institutes, senior staff from my office, and, whenever appropriate, outside consultants--is given the responsibility to define the issue clearly, prepare background briefing material and necessary analyses, develop options for consideration, and assist in the development of a detailed agenda.

One of the great strengths of the Committee is the depth and variety of perspectives that are brought to bear on an issue. To enhance and extend this capability even further, we initiated the practice of inviting a representative from each of the national advisory councils to participate as an ex-officio member. For instance, Dr. John Dowling represented this Council at the last DAC meeting on the topic of "The Human Genome." In addition to assisting us in our deliberations, this practice serves to forge a communication link with the full membership of the national advisory councils and ultimately to your own institutions and constituencies which, we hope, will assist you in carrying out your advisory functions.

Operating within the framework of this new format, the DAC has provided an important vehicle for the examination of major issues confronting NIH. For instance, the November 1984 meeting was devoted to a discussion of possible steps that could be taken to simplify the extramural awards system and foster creativity in research. At the meeting there was general agreement that actions should be taken to (1) lengthen the period of award for first-time grant applicants and (2) extend the period of award for established investigators and place additional emphasis on the "track record" as a critierion in the review of their applications. To satisy these needs, two new mechanisms have been developed:

a) the First Independent Research Support and Transition Award to provide first-time principal investigators adequate time to pursue research before recompeting for support; and

b) the Method to Extend Research in Time Award to recognize established investigators by providing stable research grant support.

In June 1985 a two-day meeting brought together representatives from large and small biotechnology firms, university scientists and administrators, and members of Federal science and regulatory agencies to discuss the role of NIH in fostering the Nation's leadership in biotechnology. There emerged from this meeting a clear consensus that the NIH can contribute best to the success of the biotechnology industry by:

a) sustaining its intensive support for basic research and research training in the underlying areas of molecular biology, genetics, and immunology; and

b) exploiting further the strong biotechnology capability that exists in the NIH intramural programs by encouraging greater interaction with industry.

Other suggestions were made which required further scrutiny. A committee of senior NIH staff was established to examine these suggestions and report back periodically to the DAC to keep it apprised of progress in this area.

At our most recent meeting in October 1986, we examined the prospect of undertaking a large-scale effort to characterize the human genome by chromosome mapping and DNA sequencing techniques. There was general agreement that this new knowledge would improve greatly our understanding of the molecular mechanisms that control gene expression and would create an extensive new science base of special importance to studies of gene therapy, the toxicology of environmental contaminants, the mechanism involved in neoplastic diseases, and the nature of autoimmune diseases. There was also agreement that the technology exists (or can be developed) to permit the accomplishment of this goal. There was, however, a broad spectrum of opinion expressed concerning the best approach to addressing this goal and the next steps to be taken. I have established a working group to consider the recommendations stemming from this meeting and to suggest, for further discussion, proposals which address these concerns.

In summary, the DAC, in my view, forms an integral part of the NIH policy formulation process. The meetings serve as public forums for discussion and debate of emerging issues in the areas of science and public policy. Committee members, ex-officio members, and invited participants--by virtue of their prominent and influential positions throughout the scientific, academic, professional, and industrial communities--serve as effective spokespersons in communicating to the NIH the views and concerns of these relevant communities and, in turn, act to inform their colleagues of proposed policies, plans, and activities of the NIH. Attendance by members of other Federal agencies, professional organizations and voluntary health groups, and congressional committees facilitates communication with these organizations. The heavy representation at these meetings by members of the scientific and lay press assures widespread dissemination of these deliberations.

I would be pleased to answer any questions you might have and also to hear your views concerning the current role and function of the DAC. Before entertaining questions, however, I thought it might be useful to provide a brief overview of the '88 NIH budget.

The FY 1988 budget request that was sent to Congress recently reflects the priority that continues to be placed on the support of investigator-initiated research project grants. The budget requests support for a total of 19,131 research project grants, 20 more than the FY '87 comparable level. These funds will provide for an average cost of approximately $164,000 per award, the same average cost as the FY '87 comparable level.

The request of $233.3 million for research training would support approximately 10,867 trainees, the same number as supported in FY '87, and a level essentially consistent with the recommendations of the National Academy of Sciences. Stipend levels would remain at the FY '85 level.

The $522.0 million requested for research centers represents a decrease of $1.4 million from the FY '87 comparable funding level although these funds

will be used to support 560 research centers, the same number as supported in the FY '87 comparable level. Most of the other NIH research mechanisms such as research grants, research contracts, research management and support, and disease control, will be maintained at approximately their FY '87 funding levels. Two exceptions are the Biomedical Research Support Grant program and the extramural construction program, both of which are proposed for elimination in FY '88.

While both of these programs have definite merit, they are considered of lower priority than the many NIH programs which provide direct support for research and training activities and, consequently, they have been eliminated in the face of budget constraints.

The NIH intramural research program would be increased slightly, about 4.3 percent above FY '87, to provide additional funding for activities related to AIDS research, and to absorb mandatory cost increases.

The FY '88 budget request also includes $20.0 million for continued support of the small and minority universities and colleges program, which is the same level as in FY '87.

REMARKS*

by

James B. Wyngaarden, M.D.**

- It is pleasure to meet with you today and to speak briefly about two topics. One of the subjects is the NIH Centennial Observance, but before I say anything about the NIH birthday, I must seize this opportunity to extend heartiest congratulations to the Board, to Dr. Lindberg, and to all who had a part in planning and carrying out the NLM Sesquicentennial Celebration. The whole affair was just right--a fitting and appropriate expression on an important occasion in the history of a truly remarkable institution.

- The National Institutes of Health officially began a year-long observance of its 100th anniversary on October 16 last year.

  - During this period there will be centennial seminars, conferences, receptions, dinners, and a variety of events here and in many locations across the United States and in other countries, providng public recognition of the role of the NIH in what is being described as "A Century of Science for Health."

    The next major Cenennial event will be the scholarship weekend program for 56 high school students chosen as outstanding by the governors of the 50 states, the mayor of the District of Columbia, and the principal territorial officials. These young people will be accompanied by the teacher who had the most influence in stimulating their interest in science. The students will be awarded a given opportunity to meet informally with some leading scientists, including Nobel Laureates from the NIH and other institutions.

  - As a culmination of the Centennial Observance three symposia will be held in connection with a reunion of NIH alumni--those scientists who at some time in their careers were researchers of officials at the NIH. I hope that any alumni here today will reserve October 15-18, 1987, to join us for the symposia and reunion.

FY 1988 Budget

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*Presented to the Board of Regents of the National Library of Medicine, Bethesda, Maryland, on January 29, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

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o The FY 1988 budget request also includes $20.0 million for continued support of the small and minority universities and colleges program, the same level as in FY 1987.

o I would be pleased to answer any questions you might have and to hear your views concerning the issues we face in biomedical research.

TALKING POINTS*

DRAFT

by

JAMES B. WYNGAARDEN, M.D.**

1. Point: In order to encourage young people to consider careers in clinical research, it is necessary to convey the full meaning of a clinical research career, in all its diversity and excitement.

o In his Presidential Address to the Association of American Physicians in 1982, John Oates clearly pointed out a common misconception--that clinical research simply refers to "technology transfer" and that the process of discovery is completed before clinical investigation is begun.

o Students need to know that clinical research itself may be a locus of discovery.

o Past winners of the Hazen Awards for Clinical Research or the Lasker Awards provide clear examples: Jesse Roth (explaining the basic defect in cell receptors in diabetes of the obese); Henry Kunkle (demonstrating the role of circulating immune complexes in disease);

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*Address on Training Students for Research Before the UCSF Faculty, Monterey, California, January 30, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Aaron Lerner (explaining the biology of benign and malignant pigment cells; Elizabeth Neufeld (elucidating the metabolic defects of the mucopolysaccharidoses; Roscoe Brady (explaining the biochemistry and developing experimental therapy in certain lipid storage diseases). Another clear example comes from Nobelists Brown and Goldstein for elucidating the LDL receptor pathway.

o In these efforts, the driving questions arose from clinical observations.

2. Point: There are many examples of student contributions to biomedical science. These may be less common now than in the past, due to increasing complexity and sophistication of science today.

o All such "discoveries" seem to stem from inquiring minds, incessant questioning, seeking out better explanations of observed phenomenon. Sir Frederick Banting summed up the situation well: "It is not within the power of the properly constructed human mind to be satisfied." Or as Baudelaire said, "Life is a hospital in which every patient is possessed of the desire of changing his bed."

o As noted by William Gibson in Creative Minds in Medicine, the story of the development of surgical anaesthesia is replete with student discovery and application. Henry Jacob Bigelow, who first described in the medical press the use of ether at Massachusetts General, had been interested in anaesthetic agents since his Harvard

College days when he was charged with the preparation of nitrous oxide used in the annual student "frolic". The "ether chart" was also introduced by two Harvard medical students, Harvey Cushing and Amory Codman. These charts, which recorded for each patient temperature, pulse and respiration, are so taken for granted today that it is hard to imagine the leap forward they represented in surgery.

o In 1982 Maurice Raynaud qualified for his doctorate in medicine upon presentation of a thesis on "local asphyxia and symmetrical gangrene of the extremities." Thus, for work done as a student, he gained lasting fame and eponymic recognition.

o Gibson recounts other examples as well: in 1916, a second year medical student at Johns Hopkins, Jay MacLean, discovered the anticoagulant, heparin. His ability to recover it from the dog's liver was a most important factor in making it available for use in transfusions. Helen Taussig began her work in pediatric cardiology while a first year student at Boston University School of Medicine, on the disposition of the muscle bundles of the heart. John Goodsir (1814-1867) came to his work in medical school with a rich background of microscopical observations on the marine forms dredged up from the Firth of Forth where he lived. His study of sponges provided many clues when he came to investigate bone growth. While an undergraduate at Edinburgh he embarked upon a study of the embryonic development of teeth, and he charted the stages through which the teeth passed until eruption was complete. This formed the basis of his later work

carried on a curator of the Museum of the College of Surgeons, Edinburgh, where he produced his monumental treatise on the development of bone in general. Even at that early date he had clearly the concept of bone builders versus bone absorbers, and of the balance that had to be struck between these two activities.

o Michael Lesch, B.A., in 1964 (the same year he got his M.D.) was first author on a paper, "A Familial Disorder of Uric Acid Metabolism and Central Nervous System Function," which appeared in the American Journal of Medicine. Interestingly, a footnote credits an NIH student research fellowship for support of Lesch and a grant from the former National Institute of Arthritis and Metabolic Diseases for support of co-author W. L. Nyhan.

o Joshua Lederberg was "c[illegible]ured" from Columbia University, where he was a respectable medical st[illegible]ent, to spend a summer in research in genetics at Yale University with E. L. Tatum, with whom he was to share the Nobel Prize.

o For all the due credit given to the role of creativity, imagination, and serendipity in scientific discovery, it is also well to remember the sage words of Pasteur who reminded us that chance favors only the prepared mind. And Sir William Osler who said, "A master word is directly responsible for all advances in medicine over the past 25 centuries. The master word is work."

3. Point: Special efforts are needed today to first seduce and then to nurture clinical investigators. Creativity and innovation in clinical research cannot be purchased; we must provide opportunities and a certain atmosphere. A key ingredient is the mentor or role model, so that the medical student serves an apprenticeship to a senior investigator. Today this more likely would be a series of apprenticeships. There have been a number of such special efforts which may provide insight.

o The University of Rochester model which called for an obligatory 5th year of medical school. This model produced a disproportionate share of clincial investigators.

o Duke University model--

o The private sector has made some important contributions: for example, with the Borden research award for undergraduates. Other parts of the private sector--for example, Pfizer and some of the major voluntary associations--have concentrated on postdocotral opportunities.

o The NIH has an array of programs aimed at clinical research, starting at the medical school level and carrying investigators on into independent research careers.

o An important component of these efforts is the need to portray to students that opportunities for structured learning exist and that it is possible to carve out a career in this field. Our own words and actions as clinical investigators are critical to the future of our profession.

o In his book, "Excellence: Can we Be Equal and Excellent Too?", John Gardner remarked that the influx of excellent new people into a given field in large part depends upon the morale of that field. And a major component of our collective morale is the optimism and encouragement we portray to newcomers and those on the brink of decision.

4. Point: Science has become complex, the methods intricate, and the training period so long that the physician even after two or three years of fellowship training, remains less well-trained than the Ph.D. scientist who has been training for a research career since the baccalaureate. The trends of the past decade reflect the progressive professionalization of biomedical research, in particular clinical research. Success for an M.D. investigator is increasingly dependent upon substantial training in the information, concepts, and methods of complex modern science.

o An NIH study of a few years ago to discover why applications to NIH for grants to conduct clinical research may either be disapproved or receive poor priority in the rating process has shown that

investigator qualifications and resources at their institutions played a very minor role in the poor ratings. Flaws in research design and conception of the hypothesis led to poor scores from reviewers. The most frequent deficiencies--faulty hypotheses and inappropriate experimental design--were the same flaws that were cited in the basic research proposals that were disapproved.

o The importance of more and better quality training for our future physician-scientists cannot be overemphasized. Recent analyses by NIH have indicated that as far as M.D. postdoctoral trainees are concerned, the longer they have trained, the more likely they are to apply for and receive an NIH research grant. Unless they have a minimum of three years of solid research training, they usually are not successful in competing for grants. For example, we have found that in programs where the median length of training is only 12 months--that incidentally accounts for more than half the people who enter the NIH training programs in clinical settings--only 20 percent of the M.D. graduates ever apply for grants, and only 10 percent are successful. By contrast, those with 30 months of training or more apply for NIH grants in 43 percent of instances. Well over half of those who apply, or 70 percent of the total, are successful. The rate is far better for M.D. fellows than for trainees; the fellows usually receive longer research training than do M.D.s on the institutional training grants.

o The message is clear--more research training, for most, yields a greater chance of success in gaining independent research support.

o It should be noted that many M.D.s who are not principal investigators on NIH grants nevertheless may be "successful" researchers. For example, we do not have adequate figures on M.D.s supported through sources other than the NIH nor do we have a good accounting of M.D.s working with NIH support other than as princiapl investigators (for example as heads of subprojects in large program project grants).

o Comparing success rates for first-time grant applicants by degree with success rates for RO1s regardless of past experience with applying for a grant shows an interesting, but not too surprising phenomenon: that applying for a grant, especially for M.D.s, is in itself an educational experience which helps them the second time around.

(show slides prepared by OPPE) (See Attached)

o Those who commit themselves for a time to research training and later decide to have a career in medical practice, however, will nevertheless benefit from their research exposure. Because medicine is derived from a number of sciences relevant to the health of individuals or of groups, physicians must be scientists to utilize these complex disciplines effectively. To be a scientist, the

physician must have more than rote scientific knowledge, or even fluency in a particular jargon. Physicans must be conversant with the processes of scientific inquiry--how data are obtained and evaluated; how hypotheses are framed, modified or discarded; the uses and limitations of inductive reasoning. In short they must understand science as an intellectual instrument which has been perfected slowly over centuries. Only in this way can they remain attentive to medical progress as a critical and independent participant. Otherwise, they will be in danger of being the passive purveyor of medical fashions. Both the spirit and rigor of science are necessary for the physician to become and remain a scholar in medicine. As Thomas Hobbes has written: "Desire to know why, and how, curiosity, which is a lust of the mind, that by a perseverance of delight in the continued and indefatigable generation of knowledge, exceedeth the short vehemence of any carnal pleasure."

5. Point: NIH has an array of opportunities designed with M.D.s in mind:

o The 6-year MSTP is considered one of our most successful in terms of building up clinical research. Seventy percent of the graduates hold positions in academic medicine. The program now supports about 675 students per year, producing more than 100 graduates annually of the type of scientist competing most successfully for R01 grant support.

o NIH also has opportunities for short-term training for students in health professional schools. These programs are based on our conviction--and some data--indicating the important role early exposure to research can play in "capturing" clinical investigators for careers in science.

o There are a number of NIH intramural opportunities. The NIH-HHMI program--now in its second year--brings about 30 medical students to NIH annually--for 9 month to year-long apprenticeships with top NIH investigators. Most of these students take this opportunity following their second year in medical school. In the Clinical Electives Program for medical and dental students, about 175 medical students use their own financing for an 8-10 week experience. The Summer Research Fellowship program accommodates about 100 medical students each year at NIH, depending upon available resources.

o There have been some new directions in the NRSA program. There is convincing evidence to show that the student who interrupts medical school for a year of research training is likely to elect a research career. Training program directors have been encouraged to use available stipend money to offer a year of research training to medical, dental, or veterinary students--one postdoctoral stipend can support two such trainees at the predoctoral level.

o Based on data showing the discrepancy between the "success" of fellows versus trainees [as measured by later career outcomes such as

publication in scientific journals, academic appointments and getting grants] and the fact that trainees in general serve shorter training periods than fellows, NIH has strengthened its guidelines for institutional training grants. We have advised program directors that all trainees should commit themselves to an initial minimum investment of 2 years of research training of which not less than 80 percent of their time is devoted to research. In addition, the guidelines also stress a stronger basic science component, and the need for a continuing plan of research development for those trainees that are initially successful and promising, and we recommend an additional 2 to 3 years of research training for such people. As a result, it is hoped that M.D. trainees will be better prepared to compete for R01 grants.

o The Research Career Development Awards--designed to help more novice investigators move toward independent research careers--includes several opportunities especially attractive to M.D.s--The Physician Scientist Award and the Clinical Investigator Award, which together support about 500 individuals annually.

Possible Slides

Slide 1: Percentage of NIH-Supported Postdoctorals Becoming NIH Grant Applicants

Slide 2: Percentage of NIH-Supported Postdoctorals Becoming NIH Grant Recipients

Not surprisingly, slide 1 indicates that a greater percentage of Ph.D. fellows apply for grants, with Ph.D. trainees neck-to-neck with M.D. fellows. M.D. trainees have been less likely to apply for grants.

Slide 2 indicates that M.D. fellows fare rather well in the system. An interesting point is that something seems to have improved the situation for M.D. trainees since about 1975. This is the time when older grants were converted to the NRSA, which carried a payback requirement. It may be that this forced students to self-select so that more of those truly interested in research were taking training.

Slide 3: First-Time R01 Applicants by Degree

This slide simply indicates that the numbers of first-time R01 applicants over the years have held rather steady for M.D.s, Ph.D.s and M.D./Ph.D.s.

Slide 4: First-Time RO1 Recipients by Degree.

This slide shows the trends for numbers of RO1 recipients over the years. Ph.D.s, of course, dominate by sheer numbers, but all three types of degree holders track fairly closely.

Slide 5: First-Time Applicants by Degree for All Mechanisms of Support.

Slide 6: First-Time Grant Recipients by Degree for all Mechanisms of Support.

These two slides again indicate that even when all mechanisms of support--in addition to RO1s--are looked at, the three types of degree holders track rather closely.

Slide 7: Success Rates of Competing RO1s by Degree.

Data indicate that all three types of degree holders are tracking very closely with one another.

Slide 8: Approval Rates of Competing R01s by Degree.

M.D.s are always a few points behind Ph.D.s and M.D./Ph.D.s, but clearly approval rates for M.D.s have climbed more recently along with those for Ph.D.s and combined degree holders.

Slide 9: Award Rates of Competing R01s by Degree.

These data are really striking, showing that for M.D.s who apply for grants and are approved, the chances of being funded are about identical to those of Ph.D.s.

Slide 10: Success Rates of First-Time Evers by Degree.

The data look a little different when we consider people applying for grants for the first time. Success rates for M.D.s are uniformly lower than those of Ph.D.s the first time around, but the gap seems to have narrowed somewhat since 1982.

Slide 11: Difference in "First-Time" Success Rates by Degree.

This slide plots the success rates of the three types of degree holders applying for the first time against an average success rate, showing that M.D.s are below the average consistently. It is notable that M.D.s seem to be improving since about 1982 and are now coming closer to that "average success rate."

Slide 12: M.D. Postdoctoral Trainees and Fellows Receiving at Least Nine Months of Support.

This slide simply shows the sheer numbers of M.D. fellows and trainees over the years. The dip in the number of fellows at 1975 indicates the changes in the NRSA. The common perception has been that M.D.s have not been successful in getting fellowships, yet there have been, in the last 10 years or so, approximately 250 new M.D. fellows annually.

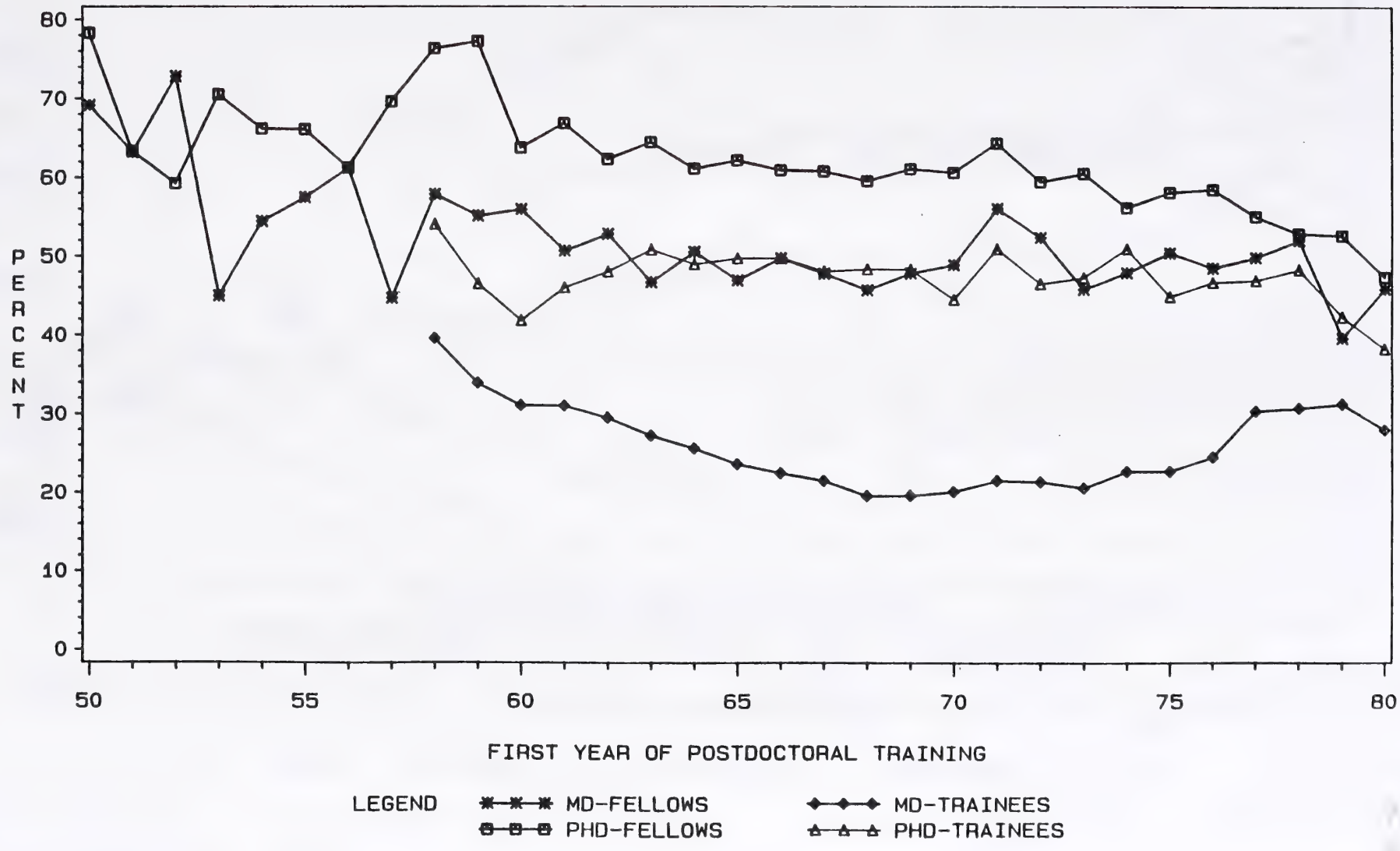
Slide 13:

Slide 14:

These indicate the total positions NIH h[illegible]llocated to one of [illegible] most successful programs, the MSTP. Cur[illegible]ly, there are about 675 individuals in the 6-year program at any given time, with about 100 graduates produced each year, of the type of scientist competing most successfully for NIH grants.

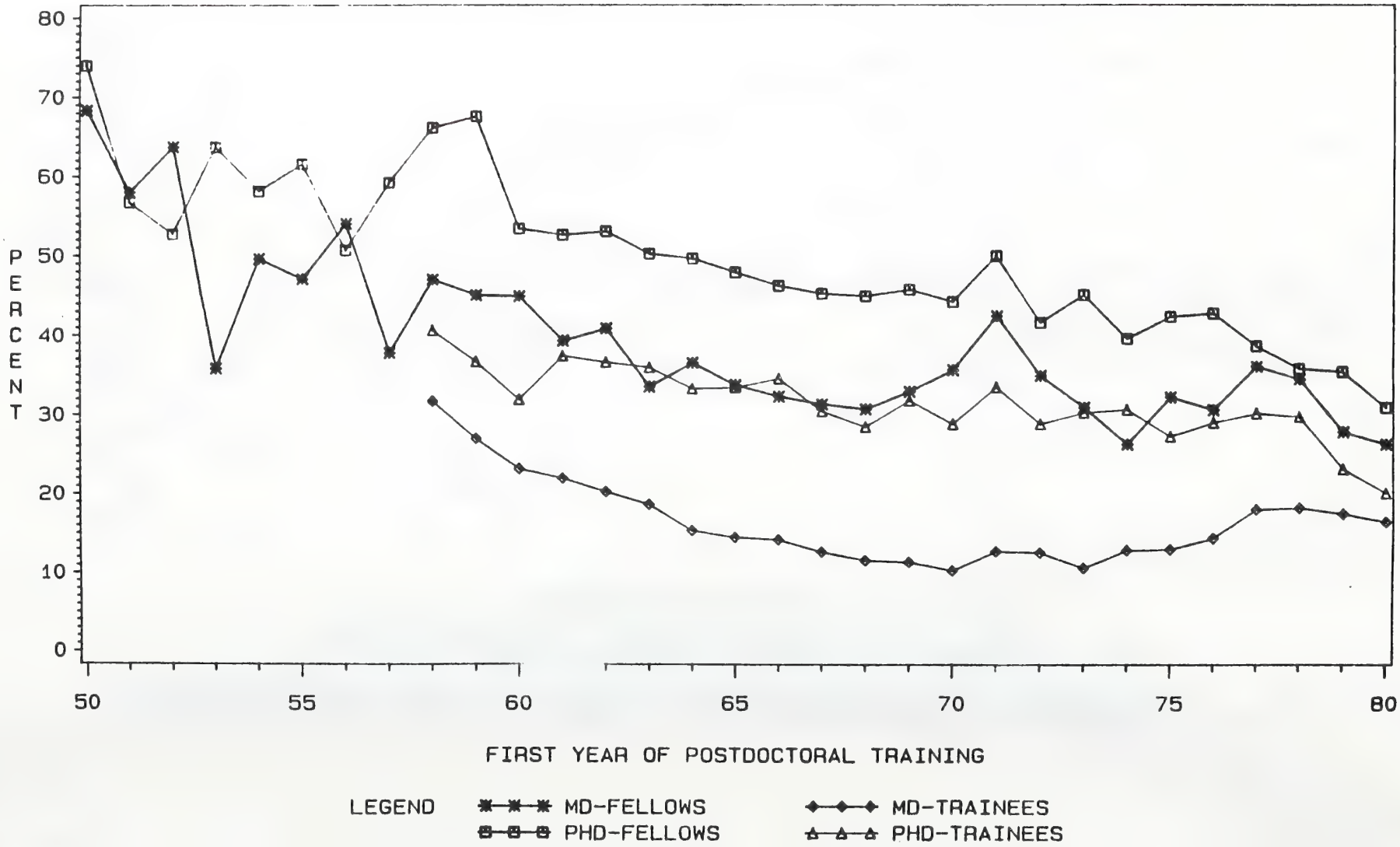
PERCENTAGE OF NIH-SUPPORTED POSTDOCTORALS BECOMING NIH GRANT APPLICANTS,

FELLOWS AND TRAINEES, MDs AND PHDs



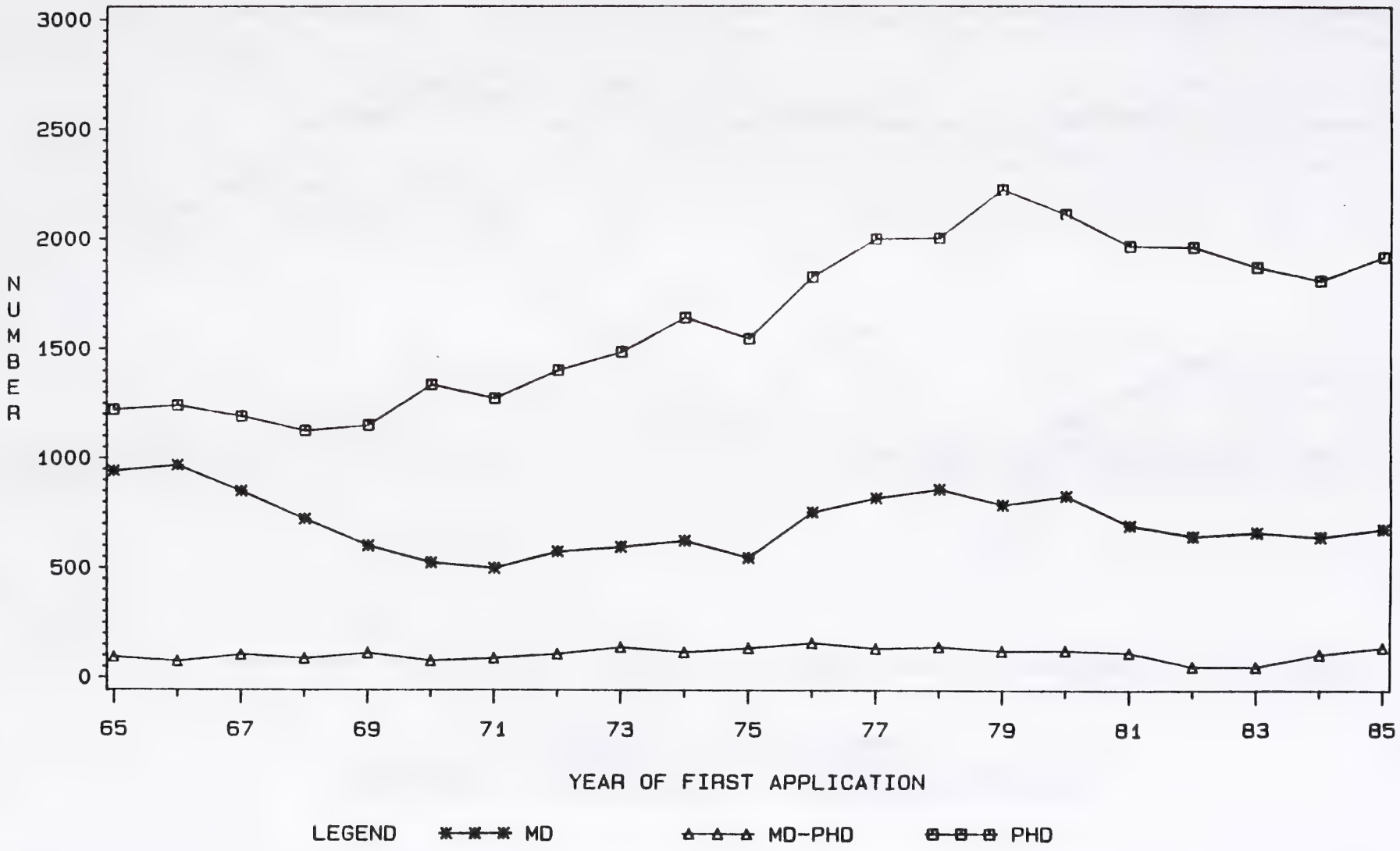
PERCENTAGE OF NIH–SUPPORTED POSTDOCTORALS BECOMING NIH GRANT RECIPIENTS,

FELLOWS AND TRAINEES, MDs AND PHDs



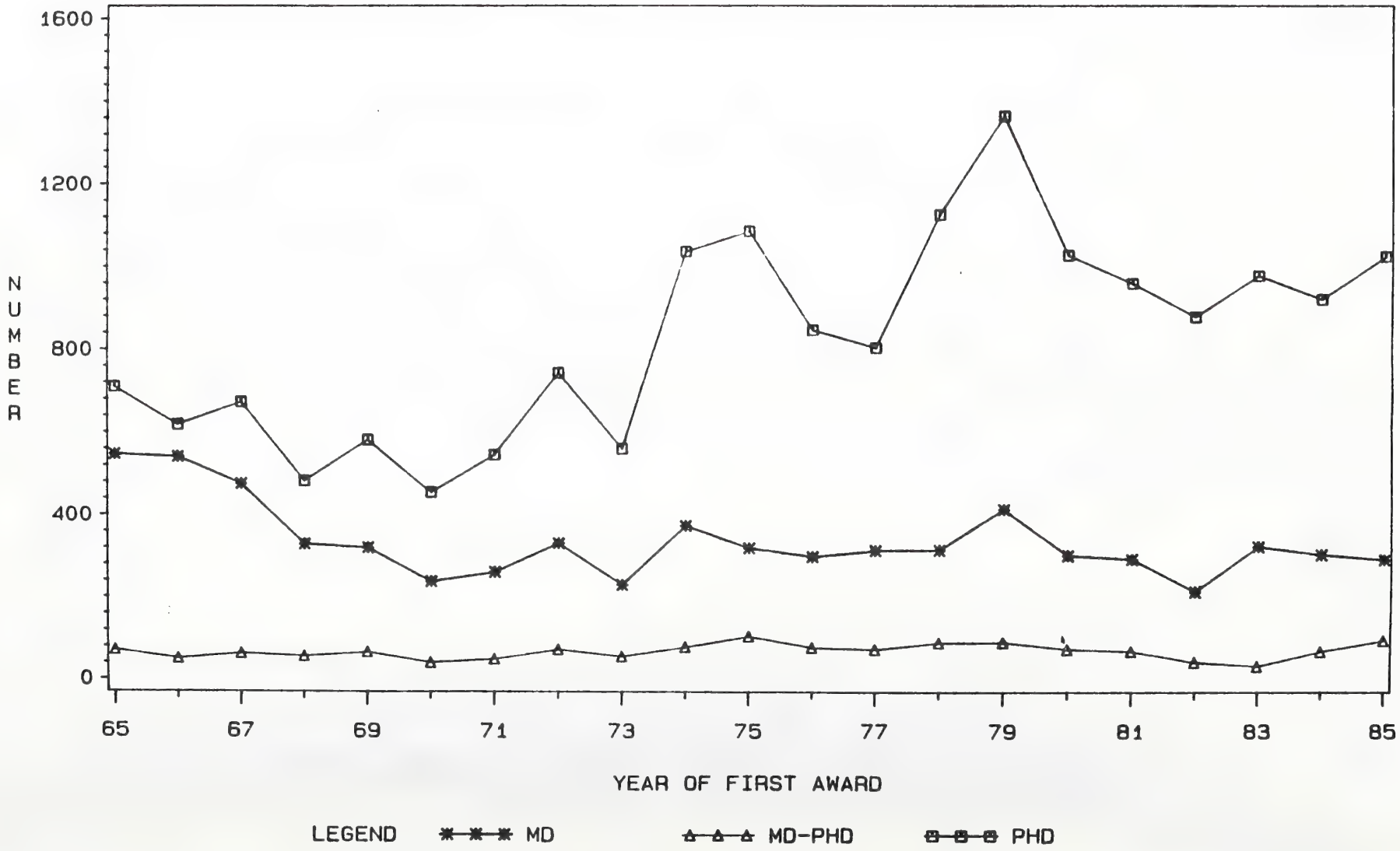
FIRST-TIME R01 APPLICANTS

BY DEGREE, FY 1965 TO 1985



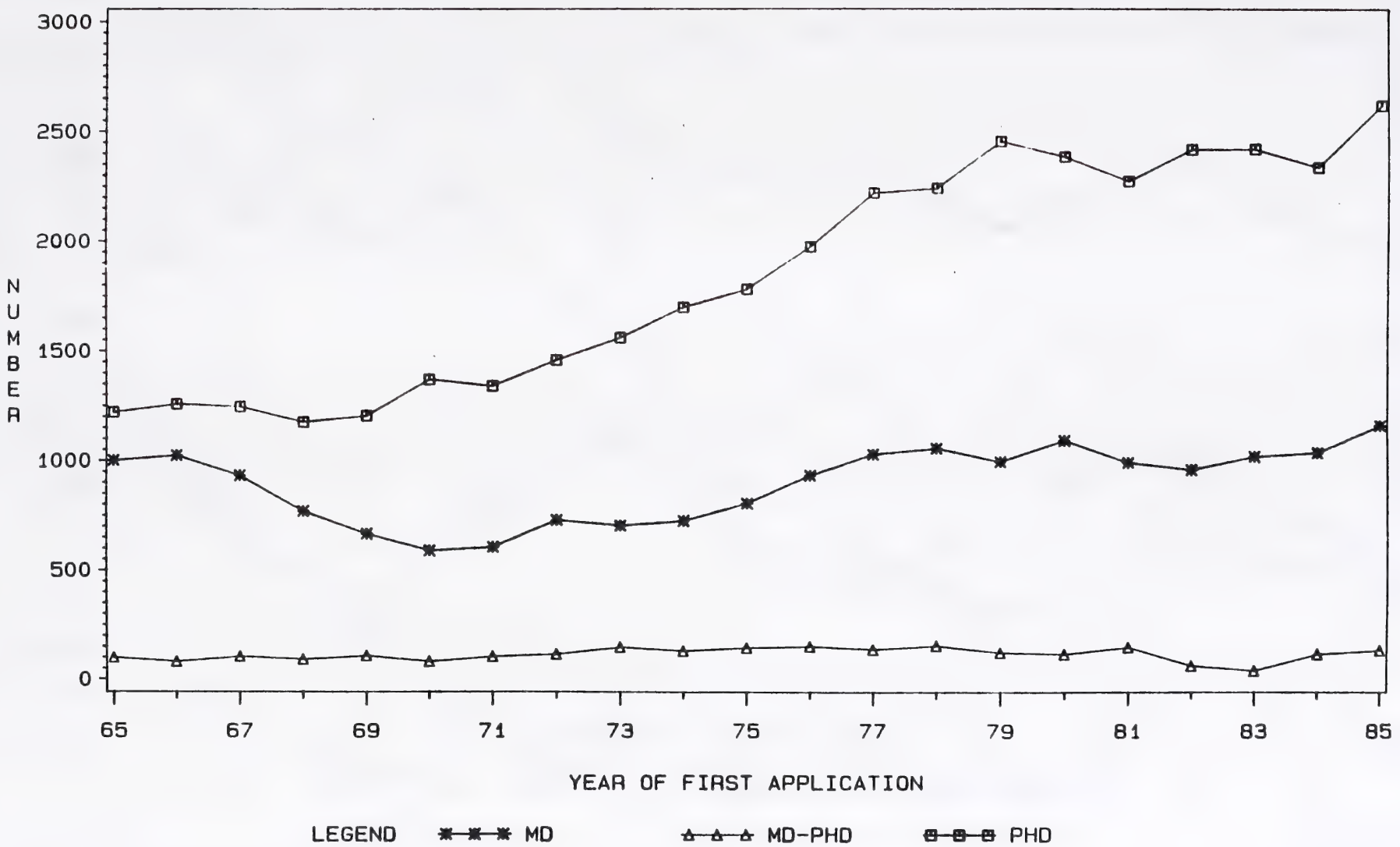
FIRST-TIME R01 RECIPIENTS

BY DEGREE, FY 1965 TO 1985



FIRST-TIME GRANT APPLICANTS

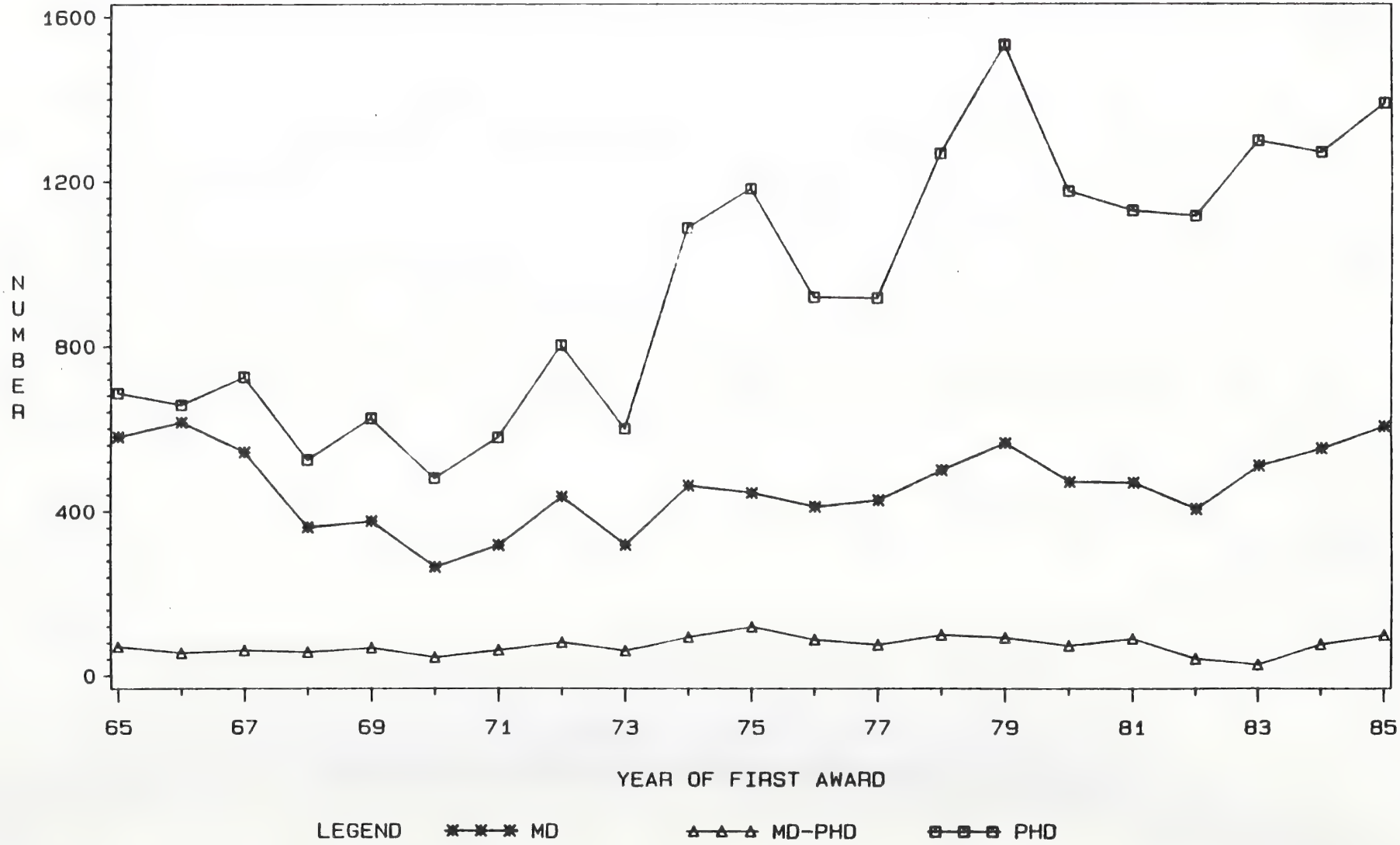
BY DEGREE, FY 1965 TO 1985



*GRANT INCLUDES R, K, M, P, U ACTIVITIES

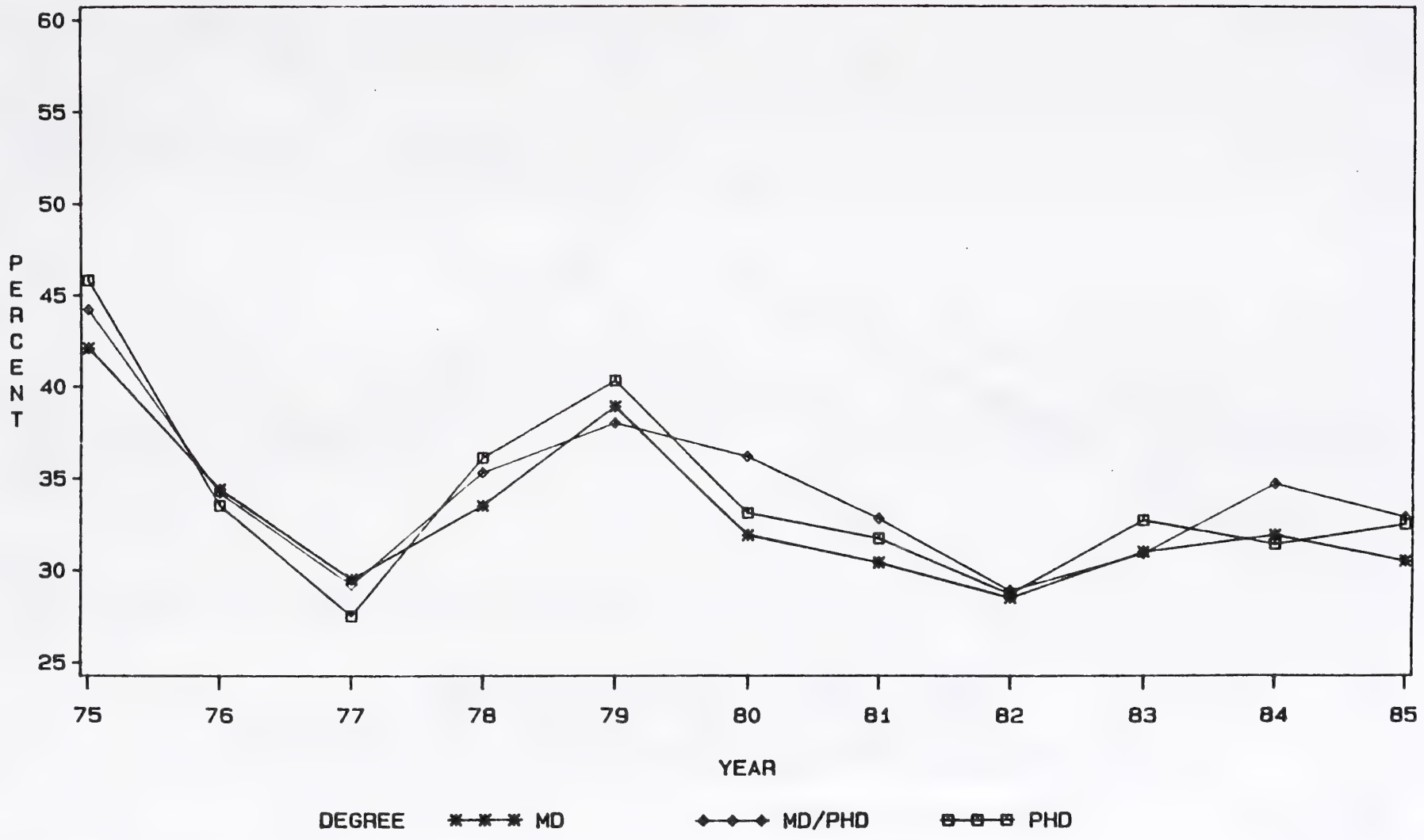
FIRST-TIME GRANT RECIPIENTS

BY DEGREE, FY 1965 TO 1985



*GRANT INCLUDES R, K, M, P, U ACTIVITIES

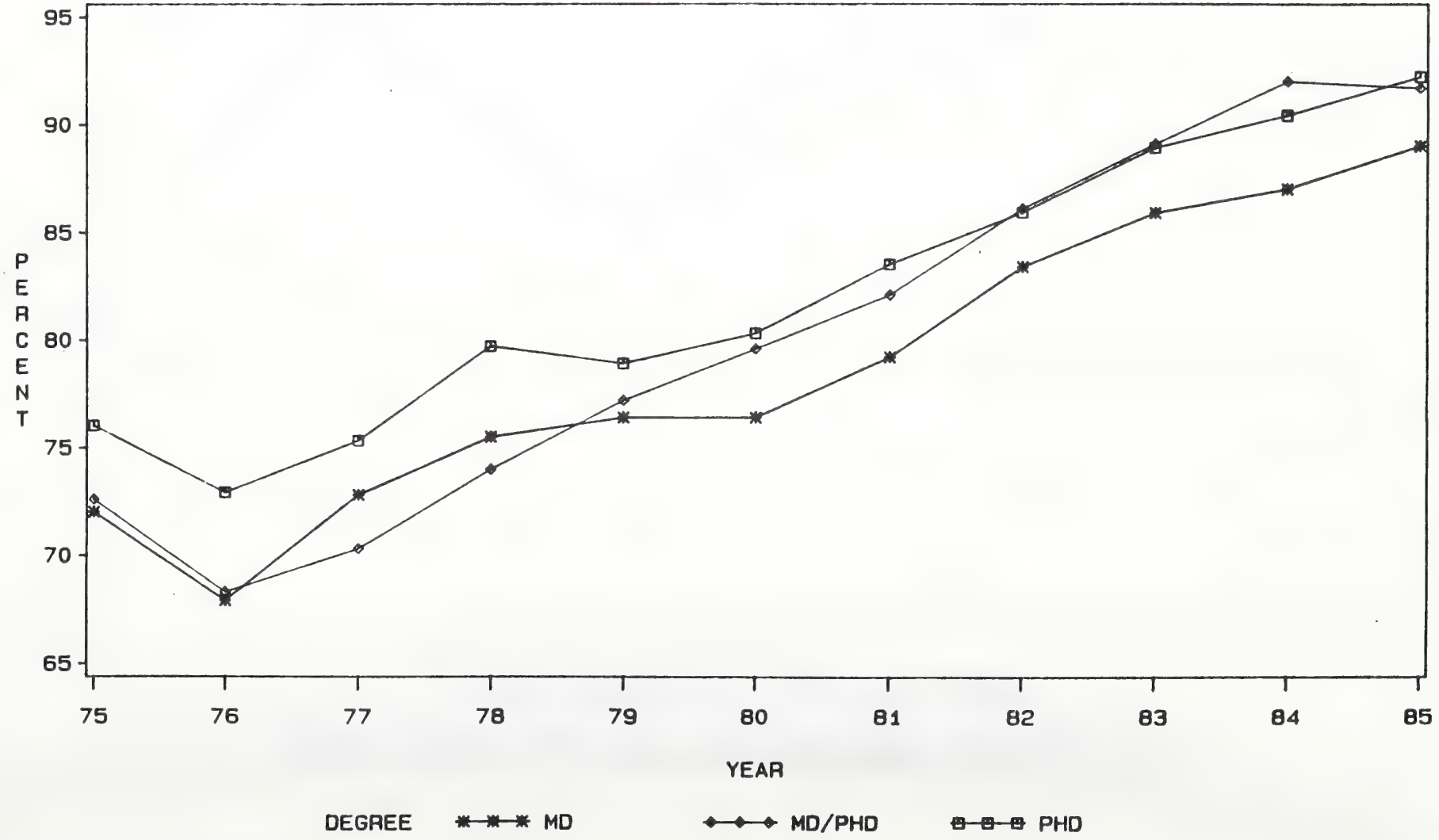
SUCCESS RATES OF COMPETING R01s BY DEGREE, 1975–85



"Competing" includes Types 1, 2 and 9

(8)

APPROVAL RATES OF COMPETING R01s BY DEGREE, 1975–85



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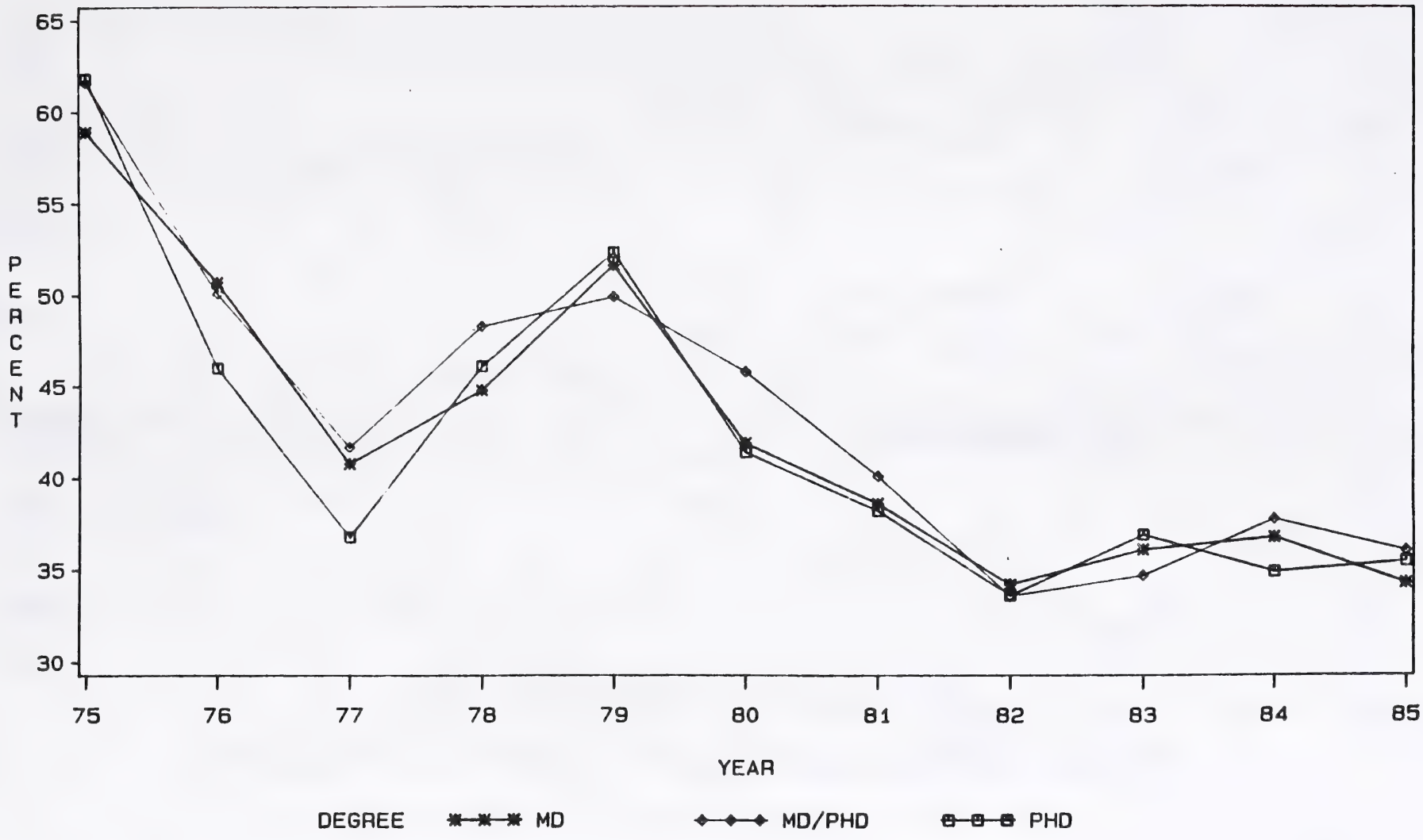
AWARD RATES OF COMPETING R01s BY DEGREE, 1975–85



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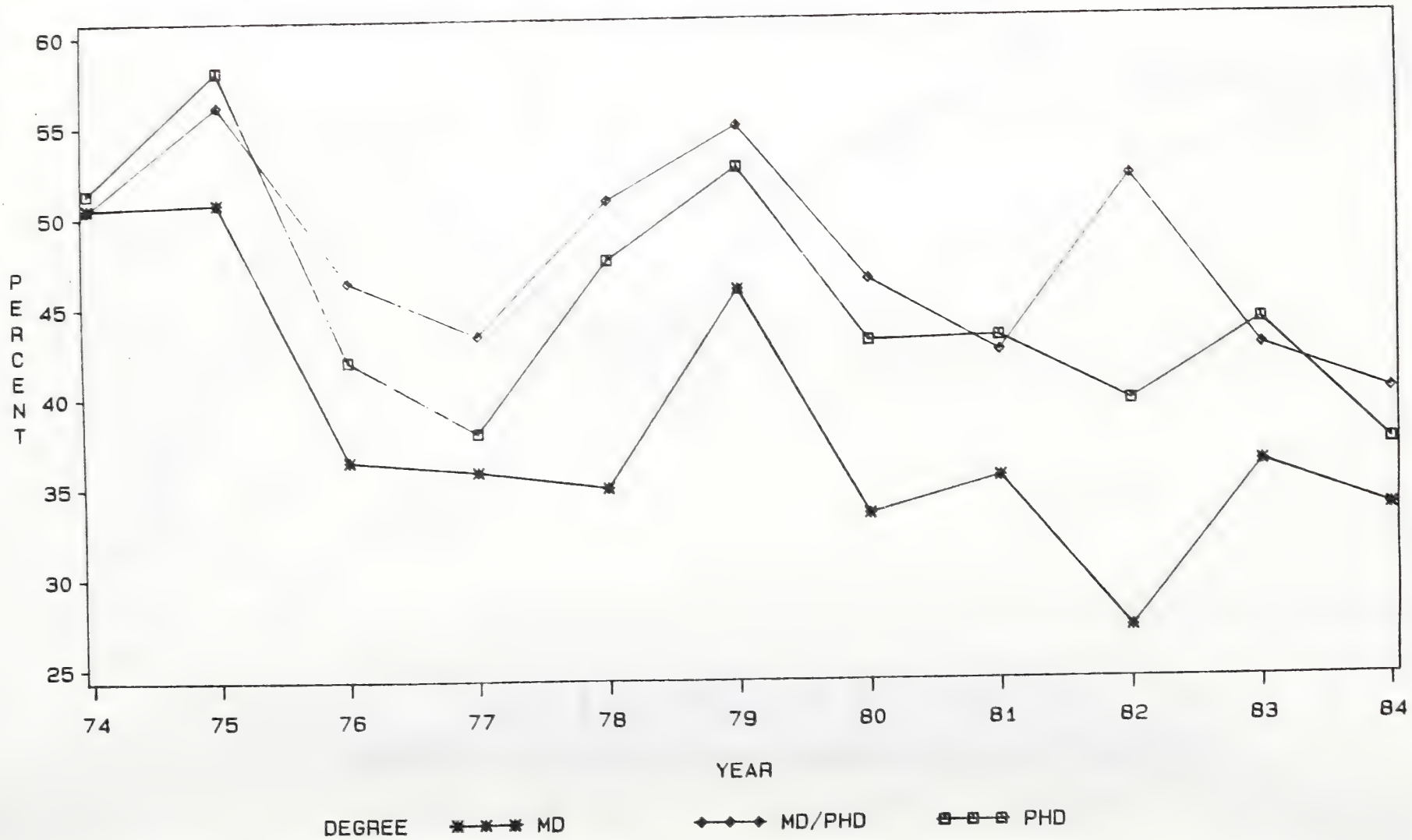
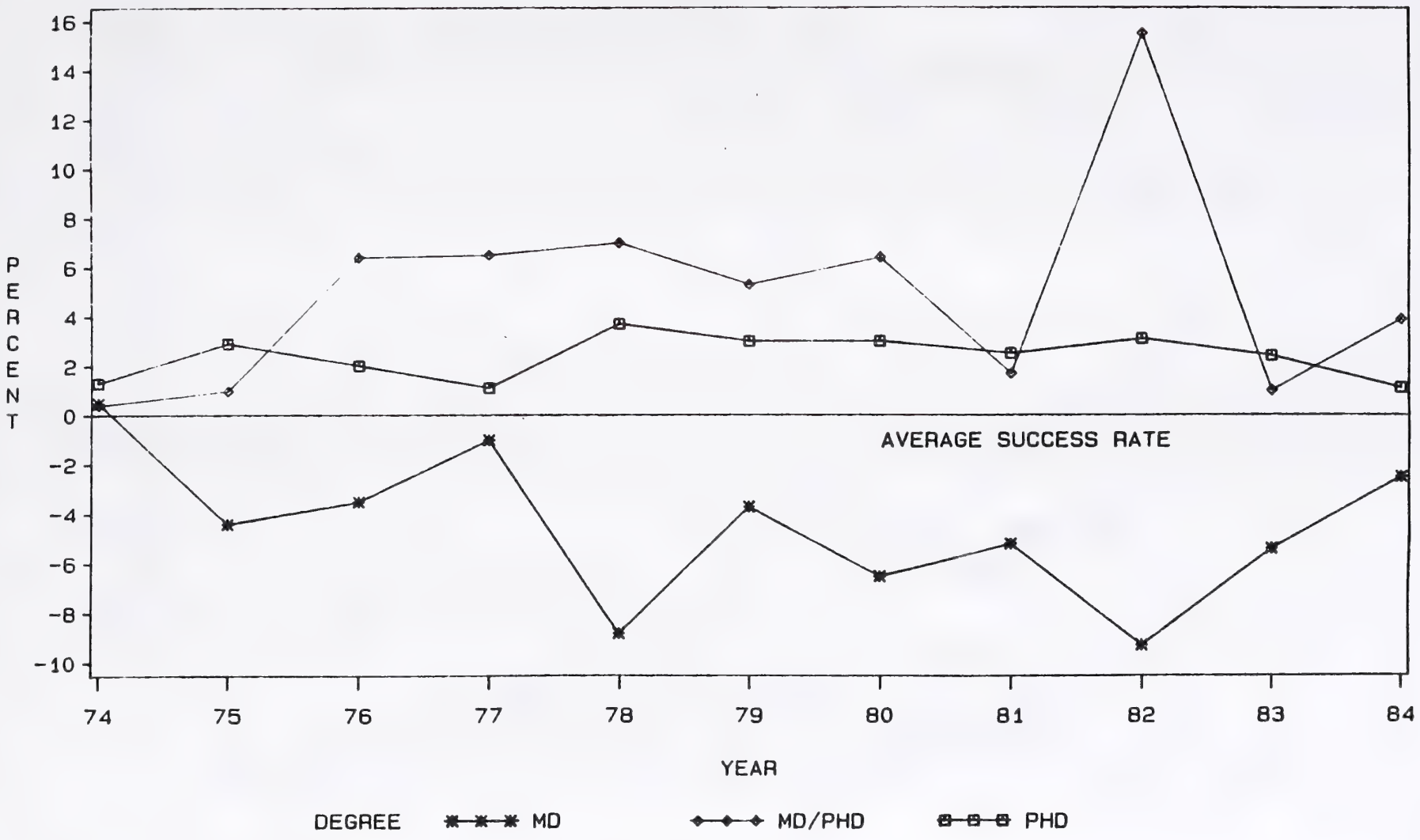
SUCCESS RATES OF FIRST–TIME EVERs BY DEGREE, 1974–84



Coverage includes Type 1 R01s

DIFFERENCE IN "FIRST-TIME" SUCCESS RATES BY DEGREE, 1975-85



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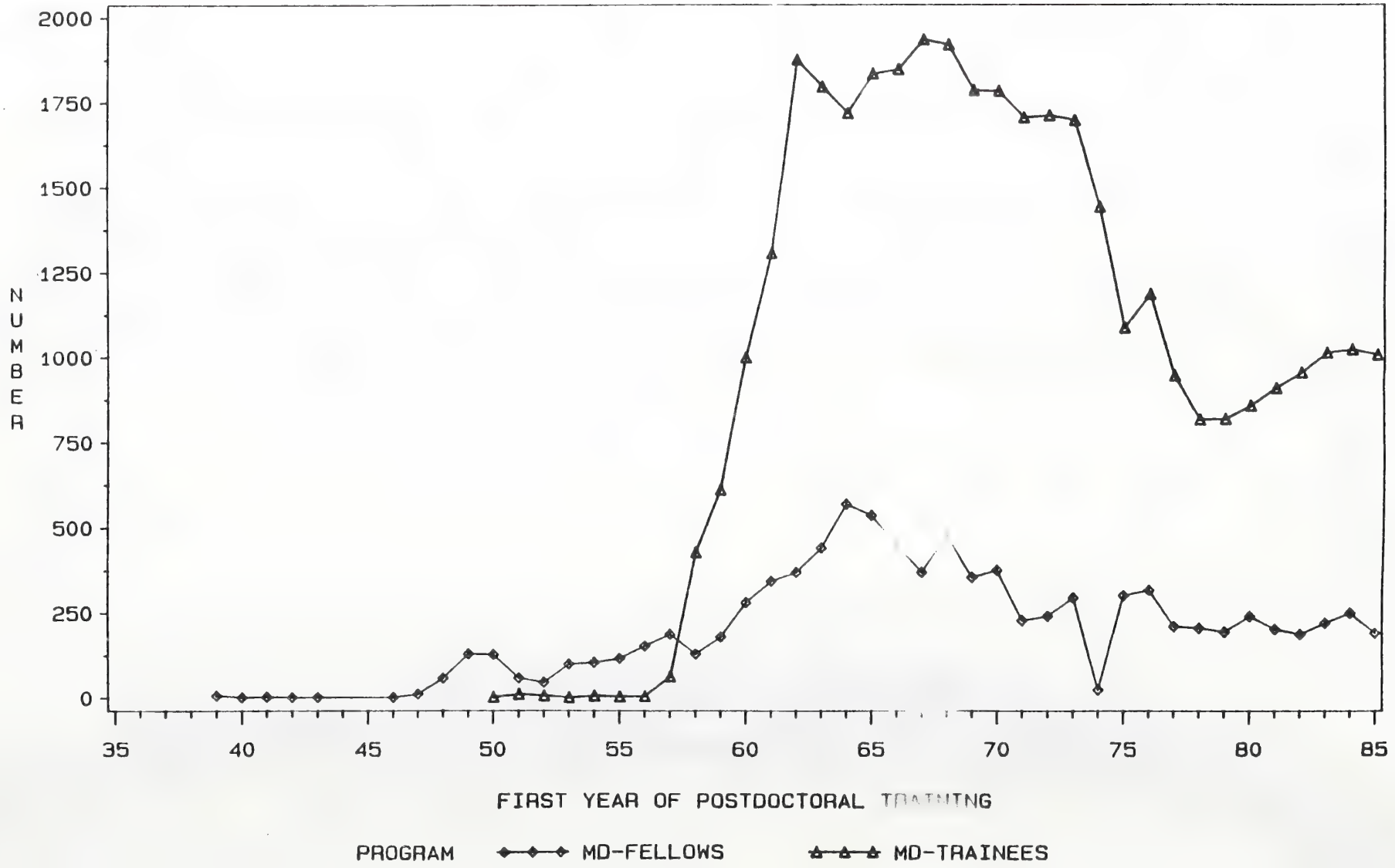
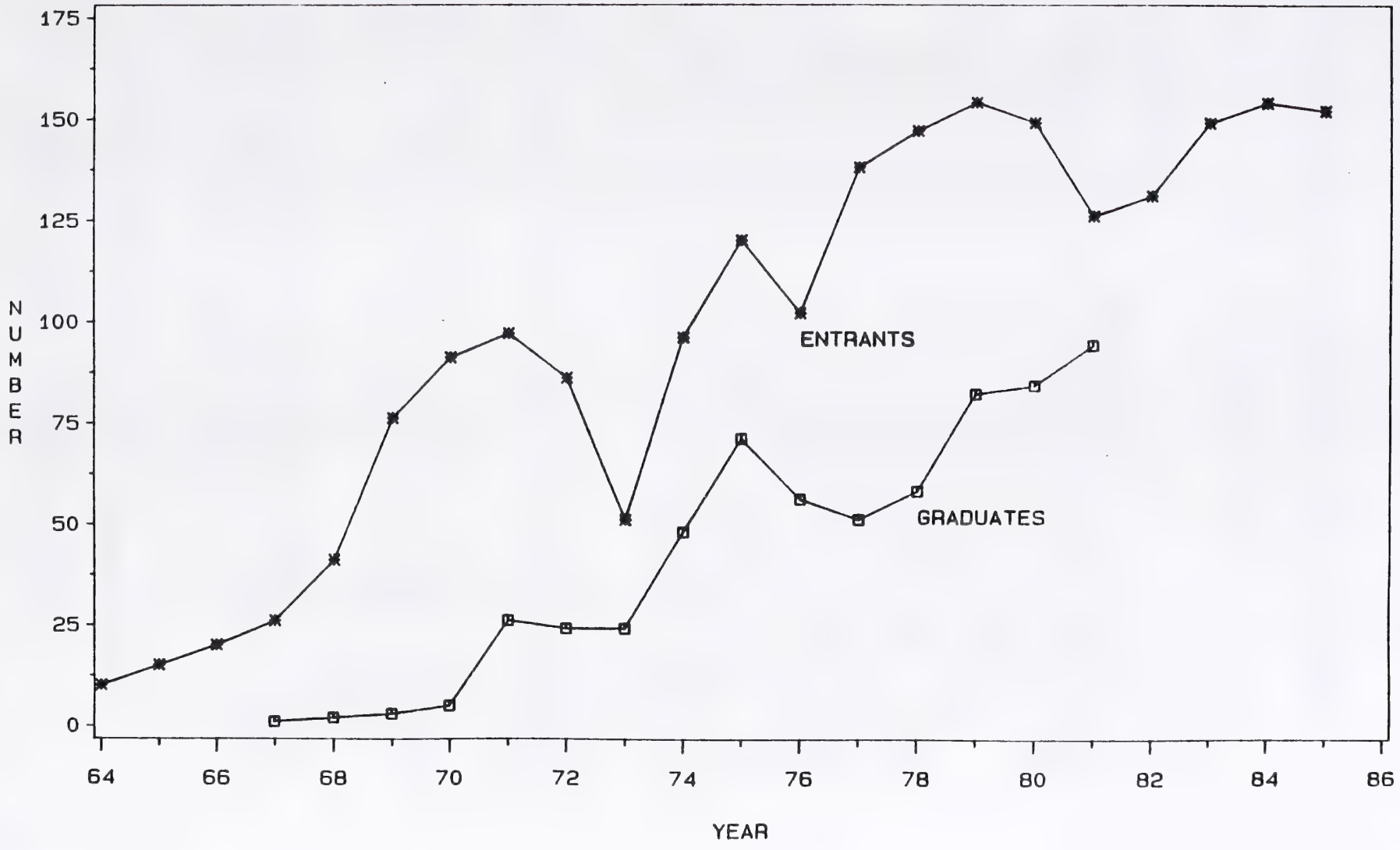
MD POSTDOCTORAL TRAINEES AND FELLOWS

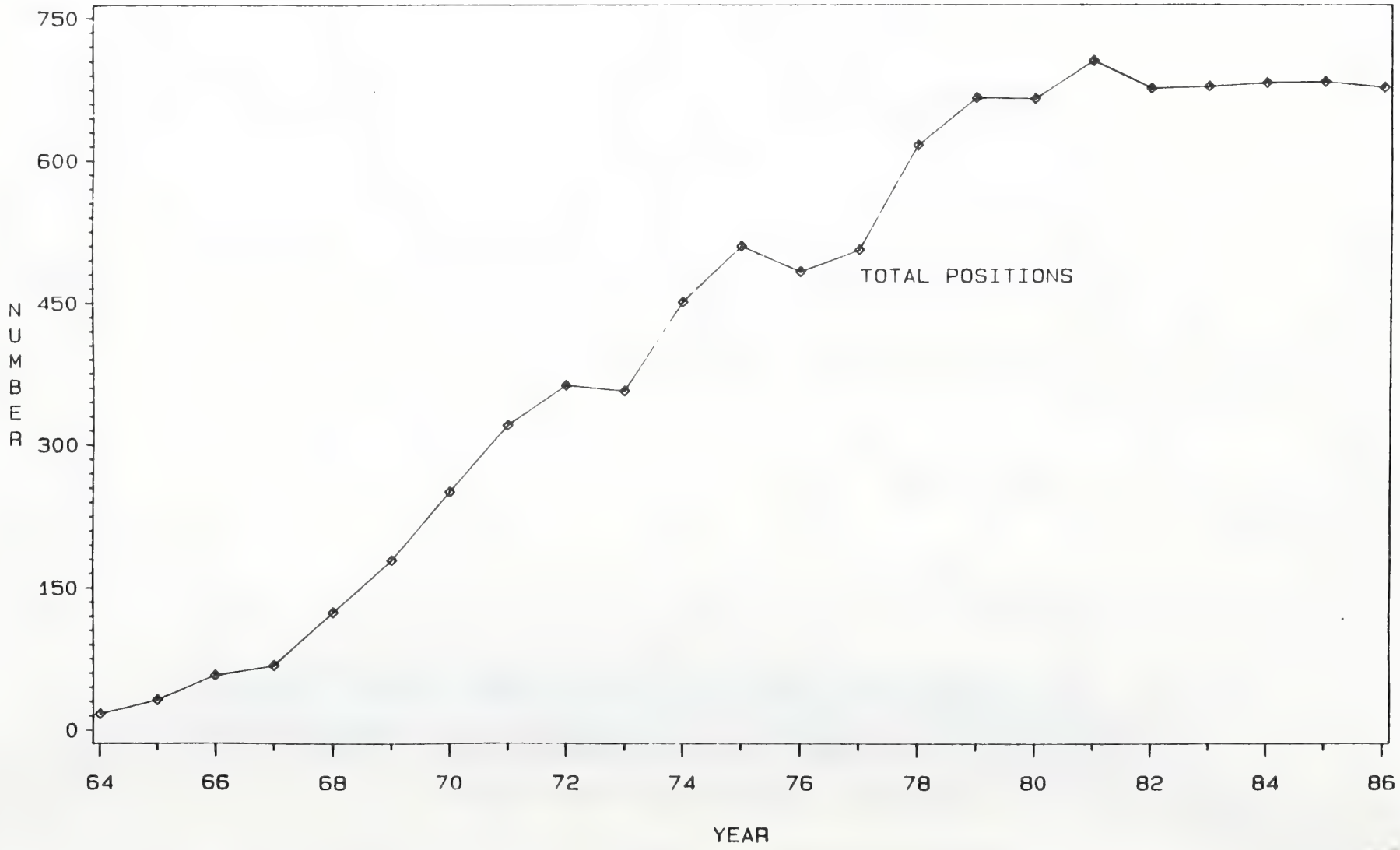
RECEIVING AT LEAST NINE MONTHS OF SUPPORT
BY FIRST YEAR OF NIH SUPPORT, 1938 TO 1985



MEDICAL SCIENTIST TRAINING PROGRAM
ENTRANTS AND GRADUATES, 1964 TO 1986



MEDICAL SCIENTIST TRAINING PROGRAM
TOTAL POSITIONS, 1964 TO 1986



THE NEW ARTHRITIS INSTITUTE--ORGANIZATION, BUDGET, AND PROGRAMS*

by

James B. Wyngaarden, M.D.**

A Centenarian and a Yearling

The NIH is in the midst of a yearlong observance of its hundredth anniversary and over the past several months it has been my pleasure to speak at many different centennial occasions and to tell a part of the fascinating history of biomedical research in this country for the past century. Today I will focus more closely on the decades of NIH research on arthritis and related diseases, but for perspective I will sketch briefly some of the significant periods in the history of biomedical research and NIH since 1887. It was in that year that a one-room laboratory was set aside for research in the Marine Hospital Service facility on Staten Island. At the beginning this Laboratory of Hygiene, that later became the National Institutes of Health, concentrated its limited resources on the devastating infectious diseases such as cholera, yellow fever, and tuberculosis. As significant progress was made on some of the communicable diseases, attention and increasing amounts of resources were dedicated to research on the chronic disabling and killing diseases. Even more significant to long-range improvements in the health of the American people has been the NIH's historical commitment to basic research. From such fundamental studies solid advances have been made in many fields that have in turn opened new vistas of future possibilities. The slogan of our Centennial observance, "A Century of Science for Health," expresses succinctly the NIH view of the inseparability of research and improvements in health.

Today, however, instead of dwelling on the history of the past hundred years, I wish to address an organization that has only recently clebrated its first birthday--the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Congressman Claude Pepper, with the authority of authorship, would maintain that the "Arthritis Institute" has in fact just celebrated its forty-sixth birthday. In remarks on the floor of the House not long ago, Mr. Pepper reminded his colleagues that the Institute was created in 1950. (Slide 1--Pepper quote).

In addition, he observed that as more and more categories of "unrelated diseases" were brought under the Institute umbrella, "arthritis has slipped further and further down the totem pole in visibility and support." To remedy this situation Mr. Pepper strongly advocated the creation of a new institute to provide a "sharp new focus" on arthritis research.

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*Presented at the Winter Rheumatology Symposium X in Snowmass, Colorado, February 5, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Beginnings of the Arthritis Programs at NIH

Thus, while technically NIAMS is a yearling, its constituent programs have been nurtured with others in an Institute that has a strong tradition of excellence. They have produced over a period of years a base of knowledge upon which we can build today with confidence and promise.

The essence of the history of an institution such as the NIH is biography. The career of the first director of the predecessor institute to NIAMS, for example, links together the two major historical eras of our agency, for he was not only an active member of the staff of the Hygienic Laboratory at the time it became the National Institute of Health, he later became Director of the National Institutes of Health.

Dr. William Henry Sebrell, Jr., who as a leading international authority on nutrition first recognized the dietary deficiency disease aribоflavinosis, began his research career at the Hygienic Laboratory under Dr. Joseph Goldberger. Dr. Goldberger's demonstration that pellagra is a deficiency disease is one of the bright chapters of NIH history.

During World War II Dr. Sebrell was codirector of the National Nutrition Program, coordinating all state agencies working in the field of nutrition. Soon after the war Dr. Sebrell was appointed as the first director of the newly organized Experimental Biology and Medicine Institute of the NIH. Then in 1950 President Truman signed the Omnibus Medical Research Act establishing the National Institute of Arthritis and Metabolic Diseases (NIAMD). The new institute incorporated the laboratories of the Experimental Biology and Medicine Institute and initiated plans for an expansion to include clinical investigations in the rheumatic diseases, diabetes, and a number of metabolic, endocrine, and gastrointestinal diseases.

Dr. Sebrell was appointed the first Director of NIAMD in November 1950 but his tenure in that post was brief because about two months previously he had been named Director of NIH, a post he held until his retirement from Federal service in 1955. We were delighted that Dr. Sebrell came to NIH and participated in the opening ceremonies for the Centennial observance last October.

In a moment I will return to a more detailed developmental history of the Arthritis Institute, but to place it in perspective, permit me now to describe briefly some of the developments in NIH history that preceded and followed the mid-1940s--a pivotal period in the history of the NIH as well as the Arthritis Institute.

A Capsule Centennial History

In 1891 the Laboratory of Hygiene was redesignated the Hygienic Laboratory and moved from Staten Island to Washington, where it operated as a small government laboratory. In 1912 the Public Health Service was established and the research program of its constituent, the Hygienic Laboratory, was expanded to include other than communicable diseases. During this period Dr. Goldberger announced his views of the cause of pellagra. Other events of that time included the establishment of the Rocky Mountain Spotted Fever Laboratory. A key event occurred in 1918 when legislation that

was passed calling for the study of veneral diseases also authorized the PHS to make grants to 25 institutions for research, thus establishing a precedent for the Federal Government to seek assistance of scientists through grants.

In 1930 the Ransdell Act redesignated the Hygienic Laboratory as the National Institute of Health, authorizing construction of two laboratory buildings and creating a system of fellowships.

In the mid-1930s a gift of 45 acres of land in Bethesda was made to the government by Mr. and Mrs. Luke I. Wilson for the use of the National Institute of Health. The headquarters building and two large laboratory buildings at the new site were completed and occupied during 1938, so that the NIH began the second half of its first century on the Bethesda campus.

It was a time of new beginnings for the NIH.

The modern era of the NIH, as well as that of biomedical research in our country, began when the Government and non-Government research laboratories, mostly in academic institutions joined their efforts in carrying out research in preparation for and during World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the members of the armed services, the Government turned to the established non-Federal laboratories for help in conducting vitally important reserach. Grants and contracts were awarded for such investigations. The arrangement worked exceedingly well. Through the newly-formed partnerships progress was greatly accelerated in research across the spectrum, from the most basic investigations to studies on how best to apply newly formulated measures for prevention, diagnosis, and treatment of disease.

By the end of the war, the U.S. Office of Scientific Research and Development was administering a large number of medically related research projects. A leading American scientist, Dr. Vannevar Bush, who was President Roosevelt's science advisor, urged that the Government continue to support in peacetime the medical research then under way in many universities, hospitals, and laboratories. At the war's end, Dr. Bush's proposal was accepted and the National Institute of Health was given the responsibility to administer the ongoing medically-related projects. This peacetime collaborative effort marked a significant change in national policy--it was a frank recognition of the mutual benefits to be realized from such a partnership--and of the long-term value of an investment in health-related research.

Dr. Bush was careful to emphasize that in the course of supporting research and training, the Federal Government should not interfere with the freedom and integrity of academic institutions. Specifically, he recommended that Government grants should allow complete independence and freedom for the scientists to determine the nature, scope, and methodology of his or her investigations. "Scientific progress," he said, "results from the free play of free intellects working on subjects of their own choice in the manner dictated by their curiosity for exploration of the unknown." It is on this philosophical foundation that the research support programs of the National Institutes of Health were established and continue to flourish.

(Slides 2 and 3--NIH Budget)

The turning point in NIH history took place in the short period of five years from 1940 to 1945, when the NIH changed from being a small Federal laboratory to an agency involved in a large way with non-Federal institutions, was more than a change in our mode of operation. Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that have been spectacular. In terms of purchasing power in constant dollars the total budget of the NIH grew from 1946 to 1968 at an astounding rate of 24 percent per year. The growth rate from 1968 to 1982, taking inflation into account, was about 2 percent per year. Beginning about four years ago, there has been a steady growth so that the 1987 appropriation exceeded the 1982 amount by $2.5 billion, or 70 percent in current dollars.

Our commitment to fundamental research has been sustained over the years --in fact, it has grown stronger. In 1970, 30 to 35 percent of our budget was for basic research. By 1980, 52 percent of our expenditures were for basic research, and by 1986 the basic research component had increased to 63 percent. This rapid increase is due in part to the priority we have given to investigator-initiated project grants and partly to a marked decline in our use of contracts for the support of research. It also reflects the accelerated pace of discovery in molecular biology, genetics, and other exciting areas.

In 1986 more than 57 percent of the total NIH budget was devoted to investigator-initiated project grants. We believe that this support mechanism fosters creativity and is an effective instrument for involving our Nation's finest scientists in the national effort to improve health through the advancement of knowledge.

A Developmental History of the "Arthritis Institute"

(Slide 4--Developmental History)

I will return now to the history of the Arthritis Institute when it was first designated as such in 1950 as the National Institute of Arthritis and Metabolic Diseases and Dr. Sebrell was its first Director concurrently with his directorship of NIH as a whole. In early 1951 Dr. Russell M. Wilder was appointed NIAMD Director. He was followed (October 1, 1953) by Dr. Floyd S. Doft, who was succeeded in November 1962 by Dr. G. Donald Whedon, who served as Director for nearly 19 years.

In May 1972 "Digestive Diseases" were given new emphasis in the Institute's mission and the name was changed to the National Institute of Arthritis, Metabolism and Digestive Diseases.

During the mid-1970s the Congress established the National Commission on Diabetes. After nine months of hearings and investigation, the Commission recommended substantial expansion of research and research training in diabetes, as well as the establishment of a National Diabetes Advisory Board. The Institute's name was changed once again to reflect the new emphasis so that, as of June 23, 1981, it became the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases. Thus, the only remaining part of the original name was "Arthritis." Dr. Lester Salans, who had headed the diabetes programs within the Institute, was named Acting Director in October 1981 and Director in June 1982. He was succeeded as Director by Dr. Mortimer Lipsett in January 1985. Dr. Lipsett served until his death in November 1985.

On November 20, 1985, P.L. 99-158 separated the Institute into the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

(Slide 5--"Authorizing Legislation")

Dr. Lawrence Shulman was named Acting Director of NIAMS in April 1986 and, on January 16, 1987, was appointed the first Director. An internationally known rheumatologist, Dr. Shulman came to the NIH in 1976 from the Johns Hopkins University School of Medicine to develop and implement the several diverse programs recommended in the "Arthritis Plan" presented to Congress that year.

A Word about the Arthritis Plan

The Plan came about as a consequence of the National Arthritis Act of 1974, whose purpose was to further research, education, and training in the field of connective tissue diseases. It mandated the appointment of a National Commission on Arthritis and Related Musculoskeletal Diseases. The Act also required centers for research and training in arthritis and rheumatic diseases, and the establishment of a data bank, as well as an overall plan to investigate the epidemiology, etiology, control, and prevention of these disorders.

After a year of study and public hearings, the National Commission issued the Arthritis Plan--a report to Congress that called for increasing research and training programs conducted by NIH; the creation of multipurpose arthritis centers throughout the country; the initiation of epidemiologic studies and data systems in arthritis; a National Arthritis Information Service; and establishment of a National Arthritis Board.

In October 1976 the Congress established the National Arthritis Advisory Board to review and evaluate the Arthritis Plan.

The organizational status of NIADDK was changed in April 1982 permitting the creation of a Division of Arthritis, Musculoskeletal and Skin Diseases. Dr. Shulman was named as Director of this Division.

Some Notables among Arthritis Institute Scientists

Pursuing the biographical component of institutional history, we must take note of worldwide recognition given to the work performed by some of NIAMD's scientists. I will mention only four examples.

Dr. Arthur Kornberg, former Chief of the Institute's Enzyme and Metabolism Section, won the Nobel Prize in 1959 for synthesizing nucleic acid.

The Nobel Prize was awarded in 1969 to Dr. Marshall W. Nirenberg of the National Heart Institute, who reported his celebrated cracking of the genetic code while an NIAMD scientist.

Dr. Christian B. Anfinsen, Chief of the Institute's Laboratory of Chemical Biology, shared a Nobel Prize in 1972 with two other American scientists for his demonstration that the three-dimensional conformation of a native protein is determined by the chemistry of its amino acid sequence.

In 1974 Dr. Baruch Blumberg was awarded the Nobel Prize for research on the hepatitis B virus protein--the Australia antigen--which he discovered in 1963 while at NIAMD.

This is only a beginning of the roster of distinguished scientists who have been a part of the Arthritis Institute through the years.

The Budgetary History of NIH Programs for Arthritis and Musculoskeletal and Skin Diseases Program

(Slide 6--Obligations for AMS Programs, 1951-Present)

As the total NIH budget has grown since 1950, the allocation of funds to programs for arthritis and musculoskeletal and skin diseases has kept pace, maintaining a share of roughly two percent of the total, and showing some increase in recent years.

(Slide 7--Major Budget Mechanisms)

About 70 percent of the budget for research on arthritis and musculoskeletal and skin diseases was allocated to grants in 1986--again closely paralleling the NIH total.

(Slide 8--Payline and Priority Scores)

The award rates for research grant applications and their paylines constitute another important measure of program activity.

(Slide 9--Allocations by Programs)

In the statistical material I have presented, the totals include expenditures for all the facets of responsibility of the new Institute. Within those totals the amount allocated specifically to arthritis is about 49 percent, to musculoskeletal research about 23 percent, to skin disease research about 15 percent, to muscle biology about 11 percent, and to training about 2 percent.

(Slide 10--Obligations for Training)

The share of the program budget allocated to training is about the same as all NIH programs (but the proportion devoted to research career development awards is substantially higher than in the other programs of the NIH).

The intramural research program for arthritis, musculoskeletal and skin diseases has been authorized 59 FTE staff members for the current year. The total of authorized FTEs for the Institute is 103. The NIAMS is currently assigned 11,000 square feet of laboratory space with the expectation of acquiring an additional 3,000.

The Mission and Major Programs of the National Institute of Arthritis and Musculoskeletal and Skin Diseases

The NIAMS has primary responsibility at NIH for extramural research and research in arthritis and musculoskeletal and skin diseases, and on the normal structure and function of joints, muscles, bones, and skin. The Institute supports a wide range of fundamental and clinical research activities and programs. Major avenues of arthritis research include the roles of humoral and cellular immune abnormalities in the pathogenesis of rheumatic disease; mechanisms by which mediators of inflammation, such as prostaglandins and leukotrienes, promote and regulate inflammatory reactions in arthritis; immunogenetic factors underlying susceptibility to arthritis; ultrastructure and pathophysiology of collagens, proteoglycans, and other components of connective tissue; and metabolic derangements underlying gout/pseudogout, and osteoarthritis.

Musculoskeletal disease research includes studies of the basic structure of bone and cartilage, metabolic bone diseases, fractures and the healing process, prostheses and relevant biomaterials, biomechanics and bioelectric phenomena, bone transplantation, the physiology of normal and abnormal gait, and inherited connective tissue diseases.

In dermatology, investigations are under way on a wide range of problems including psoriasis, acne, vitiligo atopic dermatitis, and fatal blistering "bullous" diseases. Employing new laboratory techniques, scientists are attempting to clarify the role of immunopathology, phototoxicity, and metabolic derangements in the cause of these cutaneous disorders.

The muscle biology program in the Institute supports basic research on structure and function of muscle development and regeneration of muscle, muscle energetics and metabolism, mechanisms of excitation and contraction coupling in muscle, and selected muscle diseases and disorders. Such basic studies are essential to understanding the normal physiology of muscle, how it generates energy and contracts, and the changes that occur in exercise and pathologic conditions of muscle.

Sports Medicine

The Institute supports a network of multipurpose Arthritis Centers, an Arthritis Information Clearinghouse, and an Arthritis Epidemiology and Data Systems Program. Multipurpose Arthritis Centers serve as major resources for generating new knowledge and disseminating information on the causes and control of arthritis and related musculoskeletal diseases. The Centers also demonstrate and promote the application of available knowledge for the treatment of arthritis patients. The Arthritis Information Clearinghouse serves as a nationwide source for the health professions by providing information about educational materials and programs for use in their interactions with patients, their families, and the public. The Arthritis Epidemiology and Data Systems Program serves as the administrative focus of efforts to encourage and support epidemiologic research in the field of arthritis and related musculoskeletal diseases.

Cooperative System Studies in the Rheumatic Diseases is a multi-centered organization, developed and supported in recent years, consisting of a coordinating center at the University of Utah and eight participating clinics, and supported by collaborating clinics for special studies. The investigations performed by this program include expertly planned and conducted studies of new and promising drugs and controversial treatments and natural history of disease. Well-designed systematic cooperative studies have produced important definitive information on the efficacy and safety of several anti-rheumatic drugs.

I am pleased to say that the new Council is now in place and they had their first meeting in February.

I would be happy to respond to any questions you may have.

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

Welcome to this year's G. Burroughs Mider Lecture. Selection to give this lecture, named for the late Dr. Mider is considered a mark of distinction. It is one of only two NIH Lecture Series honoring leading NIH scientists. The Mider Lectureship was established in 1968 with the understanding that it would be presented annually by an intramural scientist in recognition and appreciation of that scientist's outstanding contributions to biomedical research.

We are pleased to have as tonight's speaker a scientist who has carved out for himself a special place among his NIH colleagues. Indeed, Dr. Igor Dawid's scientific insight, leadership, and abundant contributions to his area of research have brought him international renown.

As Chief of the Laboratory of Molecular Genetics in the National Institute of Child Health and Human Development, Dr. Dawid conducts and guides research into one of modern biology's most exciting and perplexing questions: How does a single, fertilized egg cell differentiate into an organism composed of thousands of specialized cell types?

Although questions about how an embryo develops have changed little over the decades, modern laboratory tools have given us important new ways to study the molecules and mechanisms that shape a formless mass of cells into a breathing, thinking, and infinitely complex animal. In particular, DNA probes and new cell biology techniques have provided scientists with new ways to tackle these old but still intriguing questions.

Dr. Dawid and his coworkers have identified and cloned from frog embryos a set of genes, which are among the first to be expressed in the developing vertebrate. Using these genes as probes to study cell interactions and embryonic gene expression, Dr. Dawid has uncovered important new clues to the molecular mechanisms and gene products that determine how cells specialize.

Igor Dawid's early scientific interests focused on the genetic material located outside the nucleus, in cellular organelles such as the mitochondion. He was among the first to show that mitochondria contain their own DNA genome; he later helped to characterize the structure and function of this mitochondrial DNA. Dr. Dawid also extensively studied the genes the encode ribosomal RNA, a critical component of protein synthesis.

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*For Dr. Igor Dawid at the Mider Lecture on February 11, 1987, Building 10, Masur Auditorium.

**Director, National Institutes of Health, Bethesda, Maryland.

Dr. Dawid was born in Romania. He received his Ph.D. from the University of Vienna in 1960 and has held research positions at MIT with Buchanan from 1960-62, at the Max Planck Institute in Tubingen, Germany, the Carnegie Institution of Washington, Johns Hopkins University, and the National Cancer Institute. He joined the NICHD in 1982. In 1981, Dr. Dawid was elected to the National Academy of Sciences. He has received the Department's Distinguished Service Award and the Presidential Meritorious Rank Award. He also serves on the editorial boards of several molecular and developmental biology journals.

I am pleased to introduce Dr. Igor Dawid.

INTRODUCTORY REMARKS*

for

James B. Wyngaarden, M.D.**

Good morning Mr. Robinson, Dr. McNairy, Ladies and Gentlemen. Welcome to the NIH 15th Annual Black History Program. It is a pleasure to be here and to join in this observance which recognizes the contributions Black Americans have made to this nation.

Our keynote speaker, Mr. Randall Robinson, has been an advocate for human rights in South Africa for the past seven years. He is the Executive Director of Transafrica, a Black American organization concerned with United States foreign policy toward the nations of Africa and the Caribbean.

Mr. Robinson is a graduate of the Harvard University Law School where he earned a Juris Doctor degree in 1970. As a Ford Foundation Fellow, he became involved in a Middle East and African field research program where he conducted research on "the Africanization of European Law and its social impact on the population of Dar Es Salaam in Tanzania." After completing his work in Tanzania, he returned to Boston where he served as a staff attorney with the Boston Legal Assistance Project, handling a broad range of civil legal problems for members of Boston's black community. He also served as Director of the Community Development Division of the Roxbury Multi-Service Center.

In 1975, Mr. Robinson came to Washington, D.C., where he served first as staff assistant to Representative William Clay of Missouri, second as a staff attorney for the Lawyer's Committee for Civil Rights Under Law, and then as an administrative assistant to Representative Charles Diggs of Michigan.

Mr. Robinson has written numerous articles on oppression and racism in Africa for publications which include Black World, The Black Scholar, The Boston Globe, The Washington Post, and Essence Magazine. He is also the author of a book entitled The Emancipation of Wakefield Clay, published by Bogle L'Ouverture Publications of London, England.

Our speaker has been the recipient of numerous awards, including The Johnson Publishing Company Award, the Southern Christian Leadership Conference Drum Major for Justice Award, and The Congressional Black Caucus Humanitarian Award.

He is a member of the Council on Foreign Relations, the Massachusetts Bar Association, the Calvert Social Investment Fund Advisory Council, and the Board of Trustees of Hampton Institute.

It is with great pleasure that I introduce Mr. Randall Robinson.

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*For Mr. Randall Robinson at the NIH 15th Annual Black History Month Program, February 12, 1987, in Masur Auditorium.

**Director, National Institutes of Health, Bethesda, Maryland.

REMARKS*

by

James B. Wyngaarden, M.D.**

Thank you, Dr. Raub, for that wonderful introduction and thank you for your effective leadership in this NIH CFC campaign. It is so gratifying to look at the numbers achieved by the NIH this year in the CFC campaign. The grand total of $442,000 marks the first time we have ever reached and exceeded our goal.

As most of you know, this time of year is when the budget hearings begin on Capitol Hill, and we spend a lot of effort explaining where the money goes and why. It is nice to have a chart that does not need defending, it only asks to be admired.

Every single BID is represented here on stage. That is because every single BID has won at least one CFC award this year. Many have won dual awards. This was a total effort that resulted in total success.

I would like to draw your attention to page 11 and the forward in your program. That is where this campaign was won, in those individuals and units that did their best to meet the goal of "Making a Dream Come True." I wish I could congratulate each of you personally for what you have achieved. It was because of your hard work and inspired efforts that we are gathered here today.

As most of you know, CFC is the Federal partner of the United Way campaign. And the United Way campaign began 100 years ago this year. Along with Hollywood and Sears Roebuck, the NIH is sharing its Centennial with the United Way/CFC. That is particularly appropriate given our achievement this year.

In the British sport of cricket there is a term--"making a century." It refers to the rarely accomplished individual feat of scoring 100 runs in a single cricket match. The baseball equivalent is perhaps to hit three home runs in a game. I believe that this year NIH has truly "make a century." In this, our 100th year, we have achieved 100 percent of our goal.

Now, I would like to ask Mr. Don Newman, the Under Secretary of the Department, to say a few words. Many of you remember that he was one of the leading competitors in the Health's Angels CFC Run/Walk. You helped us kick it off, now help us finish the campaign. Mr. Under Secretary.

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*Presented at the NIH CFC Awards Ceremony in Masur Auditorium, February 13, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

REMARKS*

by

James B. Wyngaarden, M.D.**

The Health Policy Agenda Statement of Principles Related to Medical Science is an economically worded but comprehensive recitation of the fundamentals on which the National Institutes of Health is built. In my remarks today I will discuss some current issues pertaining to the NIH. Each of the topics involves one or more of the principles.

For example, two sentences from the Principles provide the basic rationale for the programs of the NIH. The first states "The productivity of biomedical research is dependant on continuing and long-range support." The second sentence, a part of another of the stated principles asserts "The Federal Government has the primary responsibility for assuring the viability of the nation's biomedical research effort."

The productivity of biomedical research and confidence in its promise have been responsible for the phenomenal public support that the NIH has received, especially in the post-World War II era. We are in the midst of a variety of centennial observances marking the 100th birthday of the NIH, that had its beginning in a one-room laboratory at the Marine Hospital Service Facility on Staten Island in 1887. At many of these occasions I have sketched portions of the history of the institution, its programs and its funding. Today I will refer briefly to only a part of that story in tracing the history of the NIH budget since the end of World War II.

In 1945 the Office of Scientific Research and Development, in the process of demobilization, made two important decisions. One was to continue Government support of ongoing biomedical research that had been initiated under the OSRD through grants and contracts awarded to

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*Presented at the AMA-AAAS Symposium during the AAAS annual meeting in Chicago, Illinois, February 16, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

universities, medical schools, hospitals and other laboratories throughout the Nation. The second decision was to transfer the responsibility for administration of the research to the National Institute of Health. With the reassignment of administrative responsibility the necessary funding was provided. This decision not only confirmed the role of the NIH as the principal biomedical research arm of the Federal Government, it also established extramural awards as a powerful mechanism for the support of such research.

The transformation of NIH from a small Federal laboratory, essentially self-contained, to an agency deeply involved with non-Federal institutions was more than a change in our mode of operation. Addition of the extramural dimension to the NIH was accompanied by increases in budget--increases that have been spectacular. In terms of purchasing power (that is in constant dollars), the total budget of the NIH grew from 1946 to 1968 at an astounding rate of 24 percent per year.

(SLIDE 1 -- NIH Budget FY 1945-1987 in Current and Constant Dollars)

The growth rate from 1968 to 1982, taking inflation into account, was about 2 percent per year. Then, beginning about five years ago, there has been steady growth so that the 1987 appropriation exceeded the 1982 amount by $2.5 billion, or 70 percent in current dollars.

(SLIDE 2 -- NIH Budget from 1972-1987 in Current and Constant Dollars)

The leadership responsible for the expansion and transformation of the National Institute of Health in the late 1940s and early 50s had a clear understanding of the requirement for research training. They followed explicitly the logic later embodied in the Health Policy Work Group's statement of principles to the effect that "The success of biomedical research is dependant on a population of highly trained and productive investigators." The statement continues, "The Federal Government and the private sector must continue to encourage and support the growth, development and maintenance of this corps of researchers."

Thus, concurrently with the increases in funding for biomedical research that began in that period, there were increases in the support of research training. In 1950 about 15 percent of the total NIH budget was devoted to training and fellowship grants. By 1960 the share of the rapidly increasing NIH budget expended for training had reached more than 20 percent, and in 1965 training represented more than 22 percent. A sharp decline in the proportion of the NIH budget allocated to training began in the late 1960s. This was in part because of government-wide cuts in almost every non-defense program that could be reduced, and in part because of a widespread perception that some training programs were in fact disguised specialty training. The downward trend has not been reversed, and only in the last five years has leveled out, but at about 4 percent of the total NIH budget.

There are some hopeful signs, however. Notwithstanding its decreasing share, the funding for training has remained about constant since 1980. We have been able to fund over 10,000 training positions each year, and thus to maintain roughly the number of training positions recommended by the National Academy of Sciences.

Special efforts are needed today to attract and then to nurture physician-investigators. The NIH has an array of programs aimed at clinical research, starting at the medical school level and carrying investigators on into independent research careers. We have felt these special efforts to be necessary because the trends of the past decade reflect the progressive professionalization of biomedical research, in particular, clinical research. Science has become complex, the methods intricate, and the training period so long that the physician, even after two or three years of fellowship training, remains less well-trained than the Ph.D.-scientist who has been training for a research career since the baccalaureate. We believe that success for an M.D.-investigator is increasingly dependent upon substantial training in the information, concepts, and methods of complex modern science.

Against this background it is encouraging to note recent improvements in the average success rate of physicians who are first-time applicants for

research grant awards, as well as continued gains in approval rates of program project grant applications submitted by M.D.s.

Just as the statement of principles regarding the need for research training was anticipated by the NIH decisions in the late 1940s, so also have recent developments anticipated one of the stated principles. Work Group I made the observation that "Private industry support of biomedical research is essential." The statement continues, "Private industry has applied research as its major focus, but it also must play a significant role in basic research."

During the past decade new relationships have developed between academic institutions and industry for the purpose of supporting and conducting biomedical research. Industry, academia, and the Federal Government have become increasingly involved as working partners in biomedical research. Since 1979 industry's share of national support for health-related research and development has grown from 29 percent to 39 percent, having first surpassed the NIH share in 1983.

(SLIDE 3 -- National Support for Health R & D Source -- 1976-1986)

Permit me to turn now to a matter that is of national concern, in which the National Institutes of Health has a continuing and substantial role. I am speaking of our research on acquired immunodeficiency syndrome (AIDS). Research on the AIDS virus is the primary focus. The NIH has launched a new program of basic research in structural biology with emphasis on development of antiviral substances, especially the AIDS-causing virus. This program will complement similar efforts supported by NIH and planned for implementation at universities and other laboratories throughout the country. On December 12 last year an announcement was issued to the extramural community to the effect that funds will be available for a pilot program to apply modern techniques of determining molecular structure of the virus for the purpose of developing drugs specifically tailored to attack the AIDS virus.

It is also clear that a successful vaccine development program will depend upon a greatly expanded foundation of basic knowledge concerning the AIDS virus. The developmental process for vaccines is long and we must be prepared to support adequately the basic and applied studies essential to such development.

Our budget request for 1988 includes over $343 million for AIDS research by all components of NIH, an increase of $91 million over the 1987 appropriation.

As you probably know, the Institute of Medicine of the National Academy of Sciences issued a report late last year recommending directions for public health, health care, and research on AIDS. The committee that prepared the IOM/NAS study recommended that the Federal appropriation for research on AIDS continue to increase toward a goal of at least $1 billion by 1990. A survey of NIH components that are now involved in AIDS research, or that expect to be in the near future, indicates that it is reasonable to estimate that by 1990 expenditures of a billion dollars annually for NIH conducted or supported research could be fully justified.

Finally, and because it is a matter of considerable interest within the scientific and academic communities, I will outline the highlights of the President's budget request for the NIH for Fiscal Year 1988.

The FY 1988 proposal includes an administration request for congressional approval of changes in the FY 1987 appropriation under which NIH is currently operating. This proposal which must be viewed in the context of the FY 1988 budget would result in stable funding of $5.8 billion for NIH in both FY 1987 and 1988.

The key adjustment proposed by the President is to extend the availability of $334 million of FY 1987 funds so that they could be obligated during FY 1988, and, in fact, to require that they not be obligated until after the end of the current fiscal year. This proposed carry-over would result in: (1) a decrease of about 700 competing research project grants costing $118 million; and (2) a further decrease of $216 million to lower

the cost of both competing and noncompeting research grants from the level that could be supported under the FY 1987 appropriation. This reduction in average cost, however, would only apply to research grants awarded after January 1, 1987. No adjustments will be made to research grants awarded prior to that date.

The revised budget for FY 1987, that would result from the proposed changes, would fund approximately 19,111 total research project grants, an increase of about 315 from the FY 1986 comparable level, but as I mentioned previously, a decrease of about 700 from the FY 1987 appropriated level. The revised FY 1987 estimate would thus permit funding 5,654 competing awards.

Under the revised budget, the NIH average downward negotiations for noncompeting grants would increase from approximately 4 to 10 percent, and for competing grants from approximately 6 to 14 percent. The average cost reductions vary from institute to institute. From another perspective, it could be stated that the revised budget would support a 5 to 6 percent average per grant increase over 1986.

All other NIH mechanisms would be funded in the same amounts as in the original FY 1987 appropriations. This includes funding for 560 centers, an increase of 23 over FY 1986, and 10,867 full-time research trainees, an increase of 485 over FY 1986. The funding for AIDS research, by whatever mechanism, would not be affected by the Administration's proposal to revise the FY 1987 budget.

The President's proposal for revision of the 1987 appropriation was submitted January 5, at a time when three-fourths or more of FY 1987 awards remained to be made.

Responsible management dictates that NIH operate in a manner so as to implement the President's budget policy without foreclosing the options of the Congress. We cannot assume what action the Congress will take on the President's proposal for FY 1987 or on the FY 1988 budget request. Some of

the "ifs" growing out of this situation are problems indeed, and we feel we have no choice but to follow a prudent course at this time.

If, for example, NIH should ignore the fact of the President's proposal for FY 1987 and continue to award grants at the level of the original appropriation for this year, and then the Congress should accept the President's plan, the grants we would be able to fund subsequent to such congressional action would have to absorb the entire proposed reduction. If the reduction were applied to the fourth quarter awards only, the estimated average cost reduction required would be 30 or 40 percent of recommended levels. The later in the fiscal year the issue is resolved in such a manner, the greater the downward negotiation that would be necessary.

If the Congress should reject the President's proposal with respect to 1987 but should approve the 1988 budget request, there would be a precipitous decrease in the number of competing research grants that could be awarded, down from 6,400 in FY '87 to less than 2,000 in FY '88.

In the face of these possibilities, the NIH prepared an implementation plan to carry out the budget for 1987 as proposed by the President, and this plan has been approved by the Department of Health and Human Services. Copies of the plan have been given to the cognizant House and Senate appropriations subcommittees. Grant award notices now include a statement to the effect that we have awarded the grant in an amount consistent with the proposal that was submitted to the Congress for its consideration. Awardees also are told that the amount awarded may be increased prior to the end of the fiscal year. In the event the Administration's proposal is denied by the Congress, our approach will be to return the funds to grantees the same way they were taken--that is, by restoration--to whatever the level might have been prior to the required reduction.

Let me tell you briefly about the President's budget proposal for FY 1988 itself. It calls for $5,534.3 million in new budget authority. With the extended availability of $334.4 million in FY 1987 funds, the total obligational authority for 1988 would be $5,868.7 million, an increase of $19.1 million, or .3 percent over the 1987 comparable level. The request

would support 19,131 total research project grants, 20 more than the level for the current year. New and competing renewal grants under the President's proposal would number 5,700 as compared with 5,654 in the revised 1987 budget, and 6,211 in 1986. The average cost per grant would be fixed by this maneuver about the same as in 1987, but this would be approximately 17 percent below our estimate of the commitment/recommendation levels.

The 1988 request for research training, $233.3 million, would support approximately 10,867 trainees, the same number as in the revised 1987 level.

The number of research centers would be the same in 1988 as in 1987, but with a decrease in funding support of $1.4 million from FY '87 to the new figure of $522 million.

In the aggregate, the other NIH research mechanisms--such as other research grants, research contracts, the intramural research programs, research management and support, and disease control--would be maintained at approximately their FY 1987 comparable funding levels. Two exceptions are the Biomedical Research Support Grant (BRSG) and the Extramural Construction Program, both of which are proposed for elimination in 1988. Because of the continuing interest in investigator-initiated research project grants as the most appropriate form of support and the growing concern over budget constraints, the BRSG program which provides generalized institutional support must rank as a lower priority when compared with other NIH programs. The Extramural Construction Program is also proposed for elimination in FY 1988 due to budgetary constraints and the relatively low priority of the program when compared with NIH research activities.

In a departure from the practice in former years, the FY 1988 budget also includes a request for advanced appropriations in the amount of $2,726 million to support the outyear commitments through 1994 generated by the award of competing research grants through FY 1988. Provisions are made for modest annual increases of the average costs per grant. The funds for the noncompeting continuations would be awarded on an annual basis, as they are now.

I would be pleased to respond to questions about the budget or other matters pertaining to NIH.

REMARKS*

by

James B. Wyngaarden, M.D.**

It is a pleasure indeed to welcome you as the newest members of the NIH family, and to national service as members of the National Center for Nursing Research Advisory Council. The NIH considers its various public advisory groups to be critically important to the quality of its current and future activities. This is particularly true of National Advisory Councils, not only because of the unique responsibilities they are given by statute, but even more because they bring to bear on our programs rich resources of experience and of expertise, as well as the measured views of outside observers.

You have been told that we are in the midst of a centennial year--of many observances here and elsewhere marking the exciting history of biomedical research and the NIH since 1887. It has been my privilege to meet with many groups in recent months to talk about our history. But along with the appropriate attention to a distinguished past, it is with special enthusiasm that I participate in an important "first time" event for the NIH, namely the first meeting of this advisory council that in itself is a signal that the National Center for Nursing Research is fully operational. I am aware that the Center is still headed by an "Acting Director," but what an Acting Director Doris Merritt has been! She has focused her talents, training, experience and wisdom on the subtleties and complexities of bringing a new kind of institution into being within the NIH. Doris is about as near as one even comes to being the indispensable person in this crucially important period of the Center's development, and at a most trying and tragic time in her personal life. We are all deeply indebted to her. I have been commanded to add a footnote. When the rumor reached her that I might have something to say about her work in setting up the Center, Doris passed along to me a missive. It said:

> "I prefer any references to me, however pleasant, be made only in the framework of total effort and support from NCNR staff and the BID Directors who lent their personnel, expertise and advice to get us off the ground. This was <u>not</u> a one-woman job."

Establishment of the National Center for Nursing Research is the latest of a number of actions over the past decade or so whose effect has been to broaden the spectrum of activities of the National Institutes of Health. These steps have been taken within the context of the agency's commitment to its central mission to "uncover new knowledge that will lead to better health for everyone." Creation in 1977 of the Office of Medical Applications of

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*To the First meeting of the National Center for Nursing Research Advisory Council, Bethesda, February 17-18, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Research was such a step. The recent establishment of the position of NIH Associate Director for Disease Prevention was another important move. These are seen as means for improving and facilitating the application of the fruits of research to disease prevention and patient care. Similarly, the programs of the National Center for Nursing Research, as articulated in the congressional statements of intent, will be directed primarily toward basic and applied research related to patient care, the promotion of health, the prevention of illness, and the understanding of individual family and community responses to acute and chronic illnesses and disability. It was anticipated that patient care research may also address how nursing care may be delivered most effectively and economonically. It will also engage ethical and public policy concerns that will have a profound effect on the delivery of patient care.

On every hand one can see linkages between the potential research concerns of the National Center and the research programs of the rest of the NIH: health promotion research; the relationship between biomedical and behavioral dimensions of human health; disease prevention reserach, including the identification of biomedical, behavioral, environmental, and epidemiological factors and the development or refinement of methods that enhance the abilities of individuals and families to respond to actual or potential problems; research dealing with responses to acute and chronic illness and disability across the life span; and investigations of the constellation of possibilities related to innovative approaches to the management and delivery of nursing care.

Your concerns will extend across the broad range of disciplines as they relate to health care to the entire life span. You will add a new dimension to the ongoing programs of the National Institutes of Health. I am honored and delighted to welcome you.

REMARKS*

by

James B. Wyngaarden, M.D.**

It is a delight to welcome the members and staff of the very first Council of our newest Institute. I see many familiar faces--especially from my many years in the rheumatology community--and I hope that I can eventually get to know you all.

We greatly appreciate the time and effort Council members devote to this task--as you know, the Council constitutes the vital final step of the peer review process, which is essential to the grant-awarding function of NIH and to maintaining the highest standards among projects funded. In addition, we deeply appreciate your advice and wiscom in the guidance of our programs.

I am glad to hear of the progress that is being made in staffing the Institute and getting it on its feet. Some personnel have been transferred from the parent Institute, some are newly hired for staff offices. In the meantime, I appreciate the fact that many NIDDK staff are generously devoting their time and talents to making certain that both Institutes run smoothly until such time as NIAMS can be fully independent.

Let me be the first to say "Happy Birthday" to the new Institute as its first anniversary comes up on April 8, a year after Secretary Bowen established the Institute under the provisions of the Health Research Extension Act of 1985. But as you know, the constituent programs of NIAMS have been nurtured with others in an Institute--now known as NIDDK--that has a long tradition of excellence. Indeed, our friend Congressman Claude Pepper would maintain--with pride of legislative authorship--that the "Arthritis Institute" is in fact thirty seven years old. The National Institute of Arthritis and Metabolic Diseases was established in 1950 when President Harry S. Truman signed the Omnibus Medical Research Act.

Another crucial event in the history of NIH arthritis research occurred in 1974 with the National Arthritis Act, whose purpose was to further research, education and training in the field of connective tissue diseases. It mandated the appointment of National Commission on Arthritis and Related Musculoskeletal Diseases, as well as the creation of research centers, research training, data systems, and an overall plan to investigate the epidemiology, etiology, control and prevention of these diseases.

After a year of study and public hearings, the Commission issued The Arthritis Plan, a report to Congress that called for increasing research and training programs conducted by NIH; the creation of multipurpose arthritis centers

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*To the first meeting of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council, February 18, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

throughout the country; the initiation of epidemiologic studies and data systems in arthritis; creation of a national arthritis information service; and establishment of a national arthritis advisory board. And, I am pleased to say, that the very person NIH recruited to implement these diverse programs is here with us today to lead the new institute. He is your new Director, Dr. Lawrence E. Shulman, an internationally known rheumatologist whom NIH was able to woo away from the Johns Hopkins University. I am delighted that, once again, we can call upon Dr. Shulman's vision, creativity, leadership and scientific expertise to continue the fine existing programs in arthritis and musculoskeletal and skin diseases and to develop the new activities and programs called for in the 1985 legislation. These activities include developing a new national program and plan for arthritis and musculoskeletal diseases, broadening the scope of both the data systems and the information clearinghouse to include musculoskeletal and skin diseases, and establishing interagency coordinating committees on arthritis and musculoskeletal diseases, on skin diseases and on lupus.

The new Institute's and Dr. Shulman's excellent leadership and stewardship of the nation's biomedical research efforts are already evident in two highly successful NIAMS-sponsored meetings held recently. The first was the October conference, "Molecular Biology: Its Potential for Advancing Rheumatology Research," in which several of us here had the pleasure of participating and which reviewed the enormous progress that has been made in molecular biology and identified those areas of research in arthritis and musculoskeletal disease that might most benefit from this progress.

I also congratulate you on the success of your scientific workshop on osteoporosis help at NIH just last week, which was so ably cochaired by your fellow Council member, Dr. William Peck. I know this broad and comprehensive review of the field is receiving widespread attention from both the scientific community and the public and will serve as an important guide for our research efforts in the future.

I am also proud of the success NIAMS and its predecessor programs have had in encouraging the expansion of both basic and clinical research essential to the task of understanding epidermolysis bullosa, a distressing and potentially fatal blistering skin disease with which many of you are familiar. One of youru new Council members is Ms. Arlene Pessar, a highly respected leader in the voluntary community who has so ably shown us how to move the twin mountains of the Congress and the bureaucracy and so to get more attention for this terrible disease and for the field of skin disease research in general. I also look forward to the establishment of Specialized Centers of Research, as mandated by Congress, in diseases of highest national priority--rheumatoid arthritis, osteoarthritis and osteoporosis.

In summary, I am proud in this year of NIH's Centennial, to witness the rebirth of a baby-boomer Institute--born just after World War II--to an infancy full of promise and hope that we can someday conquer the chronic and disabling diseases of the joints, connective tissues, musculoskeletal system and skin that plague so many of our citizens. I praise and thank Dr. Shulman, his staff, and this fine and distinguished Council for their leadership in this effort. And so, without further ado, let me turn this meeting back to Dr. Shulman so that you can proceed with the work at hand.

REMARKS*

by

James B. Wyngaarden, M.D.**

I am pleased to meet with you today to discuss the NIH initiative concerning the utilization of structural biology in the development of antiviral drugs. It is generally acknowleged that a continuing need exists to develop pharmaceutical agents that have as their target a specific macromolecule, or even a specific region of that macromolecule. Recent advances have, in fact, provided an unprecedented opportunity for the development of a rationale to guide the design of drugs that interact with such target macromolecules. For instance, wherever a specific nucleic acid sequence can be identified that is essential to the replication of a virus, it may be possible to develop a drug that can bind specifically to this region, thus inhibiting its function.

Great strides in x-ray crystallography, biophysics, molecular modeling, and computer graphics are contributing to new insights concerning the molecular structure of proteins, the principles governing the arrangement of atoms within a molecule, and the development of methods to modify the structure of molecules to achieve new desired properties. It appears that a special initiative is needed now tomeld these heretofore disparate disciplines and fields of study and to promote a concerted effort to provide a sound, scientific, multidisciplinary approach to the development of targeted antiviral compounds. In response to this need, we have developed an NIH program desinged to stimulate basic research and mobilize the scientific resources and capabilities that exist in both the intramural laboratories of the NIH and the university and industrial laboratories across the country. To implement this initiative, $10 million was appropriated in the FY '87 budget and a similar amount is requested in the FY '88 budget to continue the program.

This new effort is intended to build upon and extend ongoing NIH activities in this area. For instance, as you know the NIAID/NCI National Cooperative Drug Discovery Groups for the Treatment of AIDS (NCDDG-AIDS), that was initiated in 1986, provides a broad-based program that incorporates a variety of approaches directed toward the discovery of more effective therapies for the treatment of AIDS. The program is designed to include a comprehensive array of activities involving grant support for research leading to the development of new candidate anti-HTLV-III drugs, contract support for screening units to evaluate candidate drugs for in vitro anti-HTLV-III activity, preclinical testing in animals, selection of drugs for further

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*To the NCI Division of Cancer Treatment's Board of Scientific Counselors, February 19, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

testing, and phase I and phase II clinical testing conducted in AIDS Treatment Evaluation Units throughout the country. Efforts are enclouraged to exploit leads growing out of research in virology, immunology, molecular biology, protein chemistry, organic chemistry, medicinal chemistry, and pharmacology, as well as the disciplines bearing on the area of structural biology.

In addition, the NIAID has issued a Request for Applications (RFA) for research on "Biological and Biophysical Properties of HTLV-III/LAV and Related Retroviruses." The NIAID's solicitation is based on the fact that while considerable information is now available on the nucleotide sequence of the viral genome, much more needs to be known about the biological, biochemical, and biophysical properties of HTLV-III/LAV and other related retroviruses. An improved understanding of the structural properties of the env gene, for example, is essential in order to determine the mechanisms of viral attachment, penetration, and uncoating. This information, in turn, has important implications for other research focused on the development of vaccines as well as antiviral agents.

The NIAID's RFA invites applications for regular research (R01) grants to determine the three dimensional structure of envelope glycoproteins, reverse transcriptase, gag protein, and other viral components and to relate structural studies to biological, biochemical, or biophysical processes. Particularly encouraged are studies to identify biological or biochemical mechanisms of viral penetration into susceptible host cells, release of viral particles from infected cells, and regulation of biochemical events involved in the replication of these viruses or the regulation of the latent state. Collaboration with other investigators or institutions is encouraged but not essential to successful competition for these awards. The NIAID has allocated $2.5 million to fund applications in response to this RFA. The earliest possible award date is July 1, 1987.

The new NIH Targeted Antiviral Drug Program is designed to focus and intensify activities directed toward the incorporation of the growing body of knowledge in structural biology into approaches to the design of antiviral drugs. This program will have both an intramural compenent and an extramural component. The intramural part of the program was formed to capitalize on the vast array of relevant scientific talent and the unique research resources that are found in the laboratories of the NIH. The goal of this program is to deploy these resources most effectively in focusing on the development of specific drugs that inhibit viral attachment, penetration, replication, integration, and expression.

Toward this end, I have asked Dr. William Eaton of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to assemble the group, encourage and promote productive research, coordinate the activities of the various laboratories and investigators involved in the program, develop and maintain a review apparatus to assure an adequate and appropriate evaluation of all research proposals funded through this program and to report to me on progress in achieving the goals of this initiative.

On January 8, 1987, a full day was devoted to an intramural workshop to discuss the biology of the AIDS virus and to suggest approaches to the analysis of the fine structure of viral components. Subsequent to that workshop, 60 proposed intramural projects were submitted for review; these

proposals have been evaluated by a small group of scientists and a number of these will be funded soon.

In December 1986 the NIGMS published an RFA announcing the availability of new funds for a program of "Structural Biology as Applied to Targeted Drug Design for the Treatment of AIDS." This effort is intended to develop an extramural counterpart to the NIH intramural program in targeted antiviral drug design. The stated purpose of this program is to (1) stimulate the organization of multidisciplinary research groups centered around studies related to structural biology in order to develop approaches to targeted drug design; (2) carry out studies of the structure of the AIDS virus, viral proteins, and other molecules of importance to the understanding of AIDS; and (3) provide an environment for research training of graduate students and postdoctoral scientists.

It is expected that the applicant groups will have demonstrated particular strengths in several areas, including but not limited to crystallography, molecular modeling, drug design and synthesis, and virology. Proposals involving more than one organization, including industrial groups will be considered as long as an appropriate level of interaction and collaboration can be demonstrated.

We have chosen the program project award as the administrative and funding mechanism since this award can support both research projects and a core facility. We anticipate that three to five such awards will be made, for an initial period of 5 years. The start dates for these awards will be around September 1987. Informal interactions and exchanges of information among all the groups in the program is expected, and a yearly conference of intramural and extramural particpants is planned.

I would be pleased to answer any questions you might have and also to hear your views concerning the NIH Targeted Antiviral Drug Program.

A Second Century of Biomedical Research

February 20, 1987

James Barnes Wyngaarden, M.D.
Director, National Institutes of Health
Department of Health and Human Services

I am very happy to be here today to participate in this observance of the 100th Anniversaries of North Carolina State University and the National Institutes of Health. NIH salute to NCSU. As most of you know, my associations with the state of North Carolina are warm and abiding, as are my feelings for NCSU from whose School of Engineering my son is a graduate. I am especially gratified that representatives from Duke University and the University of North Carolina at Chapel Hill are also involved today, for NIH's ties to all three great institutions are close. I am impressed with the centennial logos on the program. I understand that your logo, like ours, is the result of a competition. Yours was submitted by a student in the School of Design and ours was designed by one of our nurses.

I thought it might be of interest to set the state for my talk with a light touch of history--provided by a perusal of the *New York Times* of 1887. That year saw the creation of the forerunners both North Carolina State and the NIH. Although the *New York Times* seems to have missed both occasions! In the case of NIH, it is difficult to forgive the newspaper, for our predecessors began their work in New York in the shadow of the newly dedicated Statue of Liberty--on Staten Island.

Grover Cleveland was President. Reports of labor problems were common--In New York cigar factories, workers were concerned about losing jobs to machines, and there was a great labor unrest regarding employment of foreign boatmen. The American Federation of Labor, founded by the cigarmaker Samuel Gompers, was just a year old as was the Haymarket Square Riot in Chicago.

The *Times* of 1887 was laced with reports of Indian uprisings among the Utes, Apaches and Dakota Tribes, although the last major Indian war had ended the previous year with capture by U.S. troops of Geronimo.

In the arts in 1887, Sarah Bernhardt was a great hit in "Camille," playing at the National Theatre in Washington, D.C.

Popular sports included pigeon shooting, horseracing, amateur boxing, and ice skating and bicycle racing. Adventuring then, as now, captured readers' attention--for example, a transatlantic boat race between American and British vessels, and a failed expedition to the North Pole.

Classified ads in 1887 commonly offered positions in private homes for dressmakers, chambermaids, and coachmen.

The Hotel Everrett, with a view of the Brooklyn Bridge, offered rooms at 60 cents and 75 cents a day or $3 per week.

Patent medicine ads were the most common ads to be seen in the New York Times of a hundred years ago: "Rheumatism Cured with Ayer's Sasparilla"--"Wellington Dyspepsia Tablets"--"Mme. Zadoc Porter's Curative Cough Balsam." Coca-cola, advertised as an "Esteemed Brain Tonic and Intellectual Beverage", had just gone on the market in a drug store in Atlanta.

The *New York Times* of 1887 did provide readers with science news. Reports were published each day of the November 10-12 meeting of the National Academy of Sciences, held at Columbia College. A paper on the behavior of metals under various temperatures was highly criticized by other scientists in attendance. There was a paper on a Balsalt Volcano in the Sandwich Islands, one on stellar photography, another on the effects of various colors on the nerves of the retina of the eye, and one reporting the temperature of the moon to be 122 degrees Fahrenheit. Further, according to the *Times*, and I quote "Some member of the academy spent yesterday in Thomas A Edison's new laboratory in Orange, New Jersey, examining particularly his new improved phonograph which he has lately perfected."

Hygiene and the threat of infectious diseases were of high interest to readers of that era: The Ladies' Health Protective Association was protesting the Board of Health decision to designate an area near the East River as a spot where stable manure could be dropped. A rumor of a yellow fever death aboard a steamer out of Brazil--later certified by the Health Commissioner as "Pernicious Bilious Fever"--was enough to clear the docks of working longshoremen for days. And, under a column entitled "The Work of Contagion", were listed the deaths for the week from diptheria, smallpox, scarlet fever, measles, typhoid fever, and meningitis.

This was the historical milieu in which the North Carolina College of Agriculture and Mechanic Arts and the Laboratory of Hygiene embarked on their separate missions. The college, of course, emerged through an organized grass roots push by farmers of the state, while NIH did not come to enjoy such grass roots support for many years. If I read correctly between the lines of a brief history of North Carolina State, the political struggles within the state to transfer the Land-Scrip Fund from the University to a separate land-grant institution were every bit as intricate and intriguing as the maneuvers in the U.S. Congress when NIH's early fate was at stake.

Despite the lack of overt public pressure for creating the Hygienic Laboratory, in retrospect, it is not difficult to see why this forerunner of the NIH came to be.

The late 1800s saw the dawn of scientific medicine. As William Osler noted in his essays written in 1904, "The spirit of science was brooding on the waters." A part of this was a first wave of reformation in medical schools which began at Harvard shortly after 1870 and spread over the entire country. Between 1840 and 1870 there had been a great increase in the number of medical schools, but the general standard of education--chiefly at 2-year private schools--was low. Fortunately, university authorities had begun to appreciate the importance of the infusion of science into the curricula.

As Osler put it, "Preventive medicine was an incomplete, blundering science until bacteriology opened unheard of possibilities for the prevention of disease." Once that branch of science took hold, tremendous advances were made. The theory of spontaneous generation had been overturned by Pasteur, Koch, and Cohn as recently as the 1870s, and by 1887 early bacteriologists already knew the microorganisms causing many of the important infectious diseases: TB, leprosy, typhoid fever, cholera, diphtheria, tetanus, bubonic plague.

This early blossoming of the age of scientific medicine set the stage for the start of the NIH--in the form of the one-room, one-man laboratory in the attic of the Marine Hospital on Staten Island. The location was appropriate--a port city where infectious diseases, particularly yellow fever and cholera, were thought be coming in with immigrants on steamships from Europe. Another major feature of the new Laboratory of Hygiene was its firm grounding on the work of the great men spawning the new science of bacteriology in Europe--particularly Koch and Pasteur. The Pasteur Institute, incidentally--which was founded specifically to investigate the disease rabies--also shares this one-hundredth anniversary with the NIH and North Carolina State University.

After the NIH moved in 1891 to Washington D.C., firmly underscoring the laboratory as a national resource, the laboratory became involved in many heroic and successful battles against disease. Among the scientists associated with the Hygienic Laboratory were some of medicine's heroes. For example, Dr. Howard Taylor Ricketts, whose work on Rocky Mountain spotted fever provided the key for finding the cause of one of the great plagues of mankind--epidemic typhus. Ricketts died of typhus in 1910, a victim of the organism that he had earlier described and that subsequently was named for him--the Rickettsia.

Another giant among the remarkable early members of the staff was Dr. Joseph A. Goldberger, who challenged conventional wisdom and proved that pellagra, then prevalent in the South, was not an infectious disease, but a nutritional disease caused by poor diet.

The Ransdell Act of 1930 was a landmark in NIH history. It changed the name of the Hygienic Laboratory to the National Institute of Health, expanding its concentration on infectious diseases to the broader mission of "Ascertaining the cause, prevention and, cure of disease." For his troubles, Sen. Ransdell was defeated by Huey Long. In 1938, NIH moved from the District of Columbia to a large tract of land in, what were then, rather rural suburbs in Bethesda. This move away from the bulk of government buildings to a campus tract of land in Maryland, may have played a role in the philosophic grounding that has made intramural NIH, in many ways, more like a university than a typical government agency.

For the first fifty years of its history, the NIH continued as essentially an independent, freestanding laboratory of limited size. World War II signalled the era of the "modern" NIH--the formation of strong partnerships with North Carolina State University, Duke University, the University of North Carolina at Chapel Hill, and other academic institutions around the country. In response to the sudden need for additional knowledge to deal with the health problems of the armed forces, the military had little choice but to turn to established nonfederal laboratories. By grants and contracts, most American scientists not in the federal service were mobilized for support of the war effort. The arrangement worked extremely well. The new partnerships greatly accelerated biomedical research and development across the spectrum from the most basic studies to the widespread of new means for prevention, diagnosis, and treatment of disease.

NIH has proceeded along a course that, in many ways, was charted by a report written in 1945 by Vannevar Bush, the President's science advisor, which greatly influenced Congressional action in the immediately succeeding years. This report, "Science--The Endless Frontier," outlined policies for federal support of health research that have served the national interests well since that time. The flavor and substance of the document stand up in sturdy perspective when viewed with the critical hindsight of more than 40 years. I would like to read a few key sentences from it:

> The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge.

Thus, back in 1945, Vannevar Bush laid the groundwork for the federal government-academic partnership in the pursuit of excellence in science. Support of biomedical science during the past three decades, chiefly by NIH, has transformed our knowledge and understanding of biology. The transformation has been so dramatic, so pervasive that it justifies the overworked term "revolution." Never in the history of biological science has there been so much exciting work going on, so many promising leads in so many fields, or such an army of brilliant scientists at work.

Molecular biology, which began in the 1950s as an exhilarating intellectual adventure in bacterial genetics, with no predictable public benefit now permeates all branches of biological science. Human insulin, interferons, human growth hormone are being produced by bacteria. Agricultural scientists--among the leaders those at North Carolina State--are exploring these applications to plant and animal improvement. The discovery of oncogenes has provided a new paradigm for cancer research.

In immunology, the once obscure flocculations and precipitations of test tube scientists have given us a wholly new insight into a range of human diseases and, in the instance of monoclonal antibodies, provides us a tool whose power is yet to be fully exploited in terms of targeted chemotherapy and even fertility control. These are impressive examples of the successes of the NIH-academia partnership as assessed at the end of our first century.

But what of the second century of science for health? Few, including myself, would chance to speculate beyond the next several years about where biomedical science will lead us, for it is the essence of science that it takes us where we've never been before and can hardly imagine.

We can safely predict, I think, that North Carolina State University, with its long, illustrious history in plant genetics, will likely continue to make great contributions in the "new" science of plant molecular genetics. Bateson, one of your great faculty members, was an important influence in my own scientific thought. Other areas of great promise are in the neurosciences, and in structural biology where we may be able to tailor drugs to elicit their pharmacological work directly on virus surfaces or cell receptor sites. The possibility of human gene therapy is not too far off into the second century, and the opportunities for mapping and sequencing the human genome are intriguing.

But how shall we--in terms of policy--make sure that the momentum of scientific discovery is maintained into the next century? Whatever the budget may dictate in terms of scientific opportunities and priorities, there are certain abiding principles at least in the foreseeable future, will guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. This is clearly seen in the case of AIDS where our tremendous advances of the past few years have been possible only because of many years of support for basic research in immunology, virology, molecular biology, and microbial genetics. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

Another guiding principle is reliance upon our partners in research--the academic institutions. During most of the history of the NIH, certainly

for the last ten or fifteen years, about four-fifths of the agency's budget has been expended in grants and contracts to other institutions for the support of research. We support scientists in institutions such as NCSU for the compelling reason that you have a national resource which there is no substitute--your faculties of trained scientists. And further, one of your central purposes is to ensure the continuing renewal of that precious resource--the trained investigator.

A third fundamental principal guiding the NIH is that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Through competing research projects, we tap the best minds for the most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information. We continue to place top priority on the award of new and competing research project grants, and on the support of such projects for the life of the award period.

A fourth principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health goals. There is a close interrelationship between research productivity and the availability and replenishment of the supply of qualified investigators.

There are some additional matters concerning the scientific community that require attention at the start of our second century. One is the need to replace the old and acquire the new increasingly sophisticated instruments needed for today's research.

Another is to address the problem of extramural laboratories and facilities that are slowly deteriorating. With the exception of funds from the Cancer Program and the National Eye Institute, NIH has not supported the construction of facilities since 1969 and now lacks legal authority to do so. This situation requires change.

A very positive aspect of this second century is one in which North Carolina State University and its sister institutions are major players. I am speaking of the entry of industry into the partnership for biomedical research. Industry's involvement with academia in research has traditionally been modest. Of all the funds going to academia for health R&D, industry's share is about three percent as compared with 77 percent from the federal government. Only relatively recently, since about 1978, has industry become a strong factor in the biomedical research coalition. The current rise of special arrangements between academic institutions and for-profit companies is not, however, a radical departure. The seemingly sudden appearance of new relationships on the biomedical scene arises from the rapid accumulation of recent scientific discoveries with practical application.

Past history of cooperation between academia and government--now with added support from industry--gives me confidence in our ability to solve current problems and meet opportunities through working together. Although we all encourage the intense competition that drives scientific

discovery, we should view ourselves as collaborators in the operation of the system that supports research efforts. NIH is vitally concerned for the health and stability of North Carolina State University, the University of North Carolina and Duke University, as I am sure, you are for the success of the NIH. The enlightened federal policy on biomedical research in this country has been unusually successful. Government and the scientific community have formed a strong and healthy partnership of cooperation in the cause of science, and the strength of this partnership will serve us well in the next century.

North Carolina State University

CENTENNIAL LECTURE SERIES

"Designing a New Century"

1986-1987

ORAL BIOLOGY AND BIOMEDICINE: MUTUAL RESEARCH OBJECTIVES*

by

James B. Wyngaarden, M.D.**

It is indeed a pleasure to join with the National Institute of Dental Research (NIDR) in celebrating the NIH Centennial. What better way to toast a history of research excellence than with a symposium that highlights achievements never dreamed of by investigators 100 years ago.

As one of the older kids on the block, the NIDR has been witness to much of the remarkable research progress that has been made over the decades. This Institute, the third to be established at the NIH, will celebrate its 40th anniversary in 1988 with a year-long tribute to the scientific advances that have molded and shaped the course of modern oral health research.

The establishment of the NIDR in 1948 provided the focal point to excite interest and accelerate progress in the prevention and treatment of oral disorders. There is no question that without the visibility of this single Federal agency to coordinate dental research within and outside the Government, there would have been no instrument to effect fluoridation studies, to demonstrate caries prevention programs, and to provide the mechanisms to support the basic research that is the rationale for all disease prevention and health promotion.

Cognizant of the intimate connection between oral and general health, NIDR research has always had a double impact. There is the direct gain in improved understanding of specific oral problems that has led to better medications, surgery, restorations and, more and more, to preventive measures. And there is the indirect gain in better understanding of general biological processes and systemic diseases.

The exploration of the oral cavity, of its bony structures, its soft tissues, its nerves, fluids and blood supply, provides a model, a living laboratory, for investigations that run the gamut of basic and clinical science. As we are well aware, oral health research is already yielding insights into major disease processes, including bone and joint diseases, inflammatory disorders, chronic pain problems, AIDS and other infectious diseases, and hereditary and developmental anomalies.

Over years, the search for better ways to improve oral health has led dental scientists into the fields of immunology, microbiology, developmental biology, genetics, and all of the other fundamental disciplines--directly into

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*Presented at the National Institute of Dental Research Centennial Symposium in Masur Auditorium on February 25, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

the mainstream of biomedical research. A glance at today's program confirms this beyond a doubt. The presentations by these seven outstanding investigators from diverse fields reflect the convergence of research interests of the dental and medical communities. As we are about to see, their findings have ready application, not only to oral health, but also to the many and complex systems that comprise man.

I want to thank these distinguished scientists on behalf of the NIH for their willing participation in this special centennial symposium--and even more so, for their outstanding contributions to biomedical research.

WELCOMING REMARKS*

by

James B. Wyngaarden, M.D.**

Welcome, colleagues.

I say colleagues because, as I mentioned in my congratulatory letter to you Centennial Scholars and Teachers, you are "Partners in Discovery." You Centennial Scholars represent the future of science, the future of American science in particular. You Centennial Teachers represent the very best of your profession, because you have demonstrated the ability to inspire excellence.

As the program progresses, we will unabashedly try to interest you Scholars in pursuing a career in biomedical research. But it is fitting that we present you with your awards in a building devoted to all of the sciences. Let me take this occasion to thank Dr. Samuel Thier for arranging for the use of the Academy as part of the program. It was a collegial gesture in the best traditions of science.

I know that for most of you Scholars, it is too early to know what realm of inquiry will ultimately be your specific interest. But, in fact, the National Academy of Sciences houses few disciplines that are not today within the realm of biomedical research. Astronomy is one field that comes to mind. However there is serious consideration of the periodicity of sun spot activity affecting the mutation cycles of influenza virus. Further, there is the burgeoning field of "space medicine" that also touches on astronomy. Mathematics, physics, chemistry, sociology, psychology, engineering -- all are now within the fold of biomedical research.

The NIH began 100 years ago as a one-room laboratory. Its founder was Dr. Joseph Kinyoun, a New York physician who journeyed to Europe and learned the then rudimentary science of bacteriology in the laboratories of Pasteur and Koch. As a matter of fact, NIH shares this Centennial with the Pasteur Institute. One hundred years ago the average American life span was approximately 45 years, and the cemeteries were full of infant graves due to an appalling array of infectious diseases. The cause of Dr. Kinyoun's founding the Laboratory of Hygiene, as the NIH was then known, was the tremendous flux of immigrants crowding New York, leading to recurring episodes of cholera, yellow fever, and other epidemics.

Today, the average life span is approaching 80 years. Most infectious diseases are under control, though the specter of AIDS gives reason to hedge that optimism. The primary killing disease in the U.S., heart disease, seems

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*Presented at the Centennial Scholars Award Presentations at the National Academy of Sciences, March 1, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

to be declining, and great strides are being made against cancer, the second leading cause of death. From one perspective it might appear that the past century of biomedical research has reached its potential and can rest on its tremendous achievements and well-earned laurels.

My perspective, however, was summarized by my good friend, Dr. Donald S. Fredrickson, President and CEO of the Howard Hughes Medical Institute. He is also the co-signer of your certificates. He said, "There is not more to be done; there is everything to be done."

Imagine sitting next to Newton as the apple fell on his head; imagine being introduced to the space program in 1959 --that is the point at which biomedical research is today. We are about to enter a revolution in our understanding of life and its processes; the technology and the core of knowledge are in place. The concepts of life, health, and human potential may be completely redefined in the next 25 years.

We have come to this point as "Partners in Discovery" with our colleagues in the pharmaceutical industry and academia. We have each helped to advance American biomedical research to the point of world leadership. Now only one thing could cause us to fail, and that would be if bright young Americans ceased to believe that biomedical research was a worthy endeavor. Whether it be at the NIH, in the pharmaceutical and health industries, or at the many outstanding universities and research institutions across this Nation, please consider the challenge of the future.

Talk to our Nobelists at lunch tomorrow, and to our scientists as you tour the laboratories of NIH. You will find that most share this view that there is "everything to do" in American biomedical research. Their colleagues in industry and academia will reinforce the same. As colleagues and "partners in discovery," I welcome you to join us.

Now it is time to present the certificates to the Scholars. We will present certificates to the Teachers tomorrow evening at a dinner sponsored by the Howard Hughes Medical Institute. As Mr. Flavin announces each student, he will also name the science teacher chosen by each Scholar.

Tom, will you please begin.

INTRODUCTORY REMARKS FOR DR. JAMES WATSON*

by

James B. Wyngaarden, M.D.**

It is Saturday morning, February 28, 34 years and two days ago. A young Chicagoan is playing with some cardboard models of protein structure in the Cavendish Laboratory at Cambridge. He probably would rather be playing tennis. The models begin to take shape in a manner that he had never considered before. The double helix structure of DNA, the "spiral staircase," the emblem of modern science is discovered that day. His British partner, Francis Crick, comes in and agrees that this is the solution. That none at the Eagle Pub, over ecstatic drinks, Crick tells everyone that "We have discovered the secret of life."

That young Chicagoan is here, Dr. James Watson. He was a radio "Quiz Kid" during his youth; he entered the University of Chicago at the age of fifteen. His first love was ornithology, but in his doctoral studies at the University of Indiana he is intrigued by the study of bacteriophages, and under Salvador Luria's tutelage he shows brillance and promise. "The Phage Group" becomes his home; Max Delbruck an additional mentor. He studies at Copenhagen and then comes to Cambridge in 1951. His book about those Cambridge days, The Double Helix, becomes an all-time scientific best seller. He wins the Nobel Prize in 1962.

"If Watson had been killed by a tennis ball I am reasonably sure that I would not have solved the structure alone, but who would?" wrote his collaborator Crick in Nature for the 21st anniversary of their paper. Fortunately we do not have to answer that question. Let us give a warm welcome to Dr. James Watson.

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*At the Luncheon for Centennial Student Scholars and Teachers and Nobel Laureates, March 2, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

INTRODUCTORY REMARKS*

by

James B. Wyngaarden, M.D.**

Good morning! Welcome to Capitol Hill and the final event of the Centennial Scholars Program. This morning, however, marks the first of a series of breakfasts planned for the remainder of this Centennial year to take place on the Hill. We will be meeting with Members of Congress and their health staff to review the remarkable progress made in biomedical science over the past 100 years, and to suggest exciting directions for the future. Topics will include the general background of biomedical research, future directions in heart disease, pediatric research, advances in cancer cell biology, aging research, neuroscience and high technology.

It is especially appropriate that the first of our breakfasts on the Hill be attended by those destined to make significant contributions to our vision of the future, and to hear from a distinguished Member of Congress concerning the expectations of the legislative branch of our government in that vision -- Senator Kennedy.

First, however, let me introduce the others joining me here at the head table. Many of you have already met Dr. Raub, Deputy Director of the NIH; Dr. Rall, NIH Deputy Director for Intramural Research; and Dr. Moskowitz, Executive Director of the NIH Centennial Activities. Joining us as well is Mr. Robert Ingram, representing our industrial partners.

In addition, all of the NIH Centennial Scholars and Teachers are represented by Daniel Hall, our Centennial Scholar from Massachusetts, and his teacher, Mr. Harold B. Simpson. They are from Hamilton-Wenham Regional High School in South Hamilton, Massachusetts.

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*At the NIH Centennial Scholars Program Congressional Breakfast, March 3, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Senator Edward M. Kennedy of Massachusetts, and his remarkable record of public service truly need no introduction. First elected in 1962, Senator Kennedy has long been dedicated to improving the health status of all Americans, and has shown great concern about access to and the costs of care. Over the years his efforts have also highlighted the importance of research as basic to improvements in our nation's health. Previously, as Chairman of the Health Subcommittee on the Senate Committee on Labor and Human Resources, an extraordinary broad range of health and social programs were under his jurisdiction. His historic partnership with his house collegue Congressman Paul Rogers produced legislation for research on cancer, heart and lung diseases, aging and many other programs. Now, as Chairman of the full Committee on Labor and Human Resources we can all anticipate that Senator Kennedy will continue to demonstrate a keen and remarkably broad interest in the programs and mission of the Public Health Service and specifically the research efforts of the NIH.

It is my very great honor to present to you Senator Edward M. Kennedy.

FOR RELEASE UPON DELIVERY

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH AND LONG TERM CARE

OF THE HOUSE SELECT COMMITTEE ON AGING

MARCH 6, 1987

STATEMENT OF JAMES B. WYNGAARDEN, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH
BEFORE THE
SUBCOMMITTEE ON HEALTH AND LONG TERM CARE
OF THE HOUSE SELECT COMMITTEE ON AGING

Mr. Chairman and Members of the Subcommittee:

Basic research involving the all-important molecules that control our life processes has been a primary concern of the National Institutes of Health over the past several decades. In its widely quoted report entitled, "Commercial Biotechnology," the Office of Technology Assessment defined biotechnology as, "any technique that uses living organisms to make or modify products, to improve plants or animals, or to develop micro-organisms for specific purposes." The fledgling field of biotechnology, in fact, owes its existence in large measure to the sustained support provided to academia by NIH in the form of grants.

Overall, NIH has supported biomedical research leading to the award of more than 70 Nobel prizes. In many cases, this research has been the basis for the new biotechnology. For example, one of the NIH Nobel Laureates, Dr. Marshall Nirenberg, of the Laboratory of Biochemical Genetics, a part of NIH's National Heart, Lung, and Blood Institute, deciphered the basic "genetic code."

NIH, with its many advisory councils and study sections, clearly considers molecular biology--and specifically research related to biotechnology--to be a top priority. Two billion dollars are now being invested collectively each year at the NIH institutes--to conduct research in biotechnology at NIH and to support it at other institutions. We classify these projects into two cateogories:

- Basic research directly related to or utilizing biotechnology includes genetic manipulation, cloning of DNA, use of special techniques to isolate and detect DNA, creation of hybridomas and production of monoclonal antibodies, and computer methods used to analyze DNA and protein sequences.

- Basic research underlying the new biotechnology includes undifferentiated, free-ranging investigations in genetics and molecular biology, cell biology, and immunology.

Among the subjects of investigation are: understanding cancer, genetics, and structural biology; clinical immunology and allergic responses; and disease prevention through vaccine production.

Most observers agree that the information derived from this research is, and will continue to be, of great benefit to human

health. For example, genetic engineering has made possible the large-scale production of therapeutically useful substances such as insulin, interferons, interleukins, growth hormone, tissue plasminogen activating factor, and blood factor VIII.

In addition, more than 35 national biomaterials resources in biotechnology are being supported by the NIH. These include banks of cells, cell products, cell fractions, and mutant organisms; archives of germ plasm; collections of DNA probes and libraries; banks of hybridomas; and national databases that provide for searching, analysis, matching, and manipulation of nucleic acid and protein sequences. These are major resources, each underpinned by the research of broad groups of investigators and supported by grant and contract awards from a number of the NIH institutes and divisions.

In response to the flood of laboratory data produced by NIH-supported research, and to aid the scientists who investigate molecular biological phenomena, NIH is funding about a dozen major computerized databases, each with its own characteristics. Some of these are at NIH, others at institutions around the United States and in other countries. Among them are the Hybridoma Data Bank, ATCC Cell/Tumor Bank, the Human Mutant Cell Repository, the Human DNA Probe Repository, Human Gene Library, Protein Information Resource, GenBank,® and the European Molecular Biology Laboratory (EMBL) Bank of Nucleic Acid Sequences.

The subject of biotechnology is of such importance that last year a meeting of the Advisory Committee to the Director, NIH, was devoted to reviewing the NIH's role in the field. Conclusions from that meeting included continued NIH support for basic biomedical research and research training, since this policy has helped earn the United States its preeminent position in the world in the area of biotechnology. In addition, it was suggested that NIH facilitate further developments in biotechnology through cooperative efforts with industry and academia and we have taken steps in this direction.

Another such meeting on a closely related topic focused on "Characterizing the Human Genome," a feat that is feasible because of advances in molecular biology and biotechnology. At this meeting, after a wide-ranging discussion, a number of conclusions were developed. For the purposes of this hearing, two are pertinent.

First, that chromosome mapping and selective DNA sequencing are the best approach to gaining an understanding of the human genome. Second, that information-handling services are absolutely necessary for optimal progress in biotechnology. Not only must new information services be developed and existing information resources expanded, but sophisticated communication linkages must be forged between resources, particularly databanks, so that researchers can have rapid and

efficient access to the totality of scientific information. These tasks are appropriate to the National Library of Medicine, an institution with a long and distinguished history in developing innovative biomedical information services.

In order to coordinate the need for access to such information with the existing resources, I established, earlier this year, a National Biomaterial Resource Committee. The five permanent members of this committee are the NIH Deputy Director (who will chair the committee), the Associate Director for Program Planning and Evaluation, the Associate Director for Administration, the Director of the National Library of Medicine, and the Director of the Division of Research Resources. One-year rotating memberships will be distributed among the Directors of the various other Bureaus, Institutes, and Divisions that constitute NIH. The charge to the committee is to coordinate the entire NIH approach to funding national biomaterial resources.

In conclusion, it is quite clear that support of biomedical research related to biotechnology will remain a subject of the highest priority at the National Institutes of Health. This heavy investment of research funds is entirely appropriate, since the potential of this field for improving human health is enormous. At the same time, we must invest in efforts to

collect, organize, and disseminate biotechnology information. Continued scientific progress demands it.

It is the consensus of those who are familiar with its work that the National Library of Medicine, at NIH, is the logical organization to undertake the building and coordinating of biotechnology information resources in medicine. The Library's pioneering use of computers to organize the world's biomedical literature offers a paradigm of the kind of new systems that must be put in place to deal with the challenges of exchanging and utilizing such biotechnological information. I am pleased that you will have the opportunity today to hear more about the role of the Library in matching the needs of the molecular biologists with the solutions resulting from advances in information science.

Mr. Chairman, members of the Committee, this concludes my prepared statement. I would be happy to answer any questions you would like to ask.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

Mr. Chairman, it is my privilege to present the President's budget proposal for the National Institutes of Health (NIH) for Fiscal Year 1988 and to report briefly on some of our activities and plans. I continue to be impressed and deeply appreciative of the interest and understanding with which you, your colleagues, and the subcommittee staff deal with matters pertaining to the National Institutes of Health.

We are nearing the mid point of a year-long observance of the centennial of the National Institutes of Health. A year ago, at our appropriation hearings, I gave a brief summary of our plans for centennial activities. I am pleased to report the high level of enthusiasm that has developed among many groups for holding special events and ceremonies to mark the 100th birthday of NIH. Between now and mid-October there is a full schedule of centennial events in Washington, as well as in many other parts of the Nation and overseas.

A consortium of leading pharmaceutical companies and the Howard Hughes Medical Institute is underwriting many of the expenses of the centennial observance, especially the four-part series of one-hour television programs being produced for airing by PBS next fall. The series, tentatively entitled "The Health Century," will tell the fascinating and significant story of the great progress that has been made in human health since the 1880s and the vital role played by biomedical research, notably the contributions made by each of the "partners in discovery," academia, industry and the NIH. We are confident that the centennial events and programs will create a better public understanding of the importance of biomedical research and will cause bright young people now making their career choices to consider the satisfaction and value of biomedical research.

During the past year the National Library of Medicine (NLM) also reached a significant milestone--its 150th birthday. The NLM continues to exercise worldwide leadership in scientific communication and is the central resource of our Nation's biomedical information system.

Since we appeared before this Committee to discuss the budget estimates for FY 1987, the NIH has completed the establishment of a new institute, a new national center, and a major new position, all of which were authorized by the Health Research Extension Act of 1985 (P.L. 99-158).

The National Institute of Arthritis and Musculoskeletal and Skin Diseases was established officially April 8, 1986, and on January 16 of this year, Dr. Lawrence Shulman was appointed as the first director of the new institute. The National Center for

Nursing Research was established April 18, last year. The programs of the NCNR will be directed primarily toward basic and applied research related to patient care, the promotion of health, the prevention of illness, and the understanding of individual family and community responses to acute and chronic illness and disability. Another important addition to the NIH organization is the establishment of the Office for Disease Prevention, and the appointment of Dr. William Friedewald as an NIH Associate Director to head the new office. Dr. Friedewald, who has been at NIH for 20 years, is an outstanding scientist/administrator who will have a major role in promoting disease prevention programs within the NIH.

Mr. Chairman, the budget proposal for FY 1988 once again underlines the importance the NIH attaches to research on the acquired immunodeficiency syndrome (AIDS). The AIDS program at NIH supports basic, applied, preclinical, and clinical research with emphasis on natural history, pathogenesis, vaccine development and treatment. Research on the AIDS virus is the primary focus. A major accomplishment of the AIDS program during the past year was the identification of azidothymidine (AZT) and its early testing in patients with penumocystis carinii pneumonia.

The NIH has launched a new program of basic research in structural biology with emphasis on the development of antiviral substances, especially against the AIDS-causing virus. Our intramural scientists will use the methods of structural biology to characterize the AIDS virus at a molecular level in efforts to develop and modify targeted antiviral drugs. This program will complement similar efforts supported by NIH and planned for implementation at universities and other laboratories throughout the country. It is clear that a successful vaccine development program will depend upon a greatly expanded foundation of basic knowledge concerning the AIDS virus.

The FY 1988 request includes $343.5 million for AIDS research by all components of NIH, an increase of $91.0 million over the FY 1987 appropriation.

Molecular biology has progressed to the point where it is now possible to characterize the genetic material of man, in other words the whole human genome, by obtaining complete information on the location of particular genes as well as the order in which their 3 billion chemical building blocks (called nucleotides) appear. The possible benefits of characterizing the human genome are tantalizing. The new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and of the molecular basis of many inherited and "orphan" diseases. We could gain substantial information on cancer as well as on autoimmune and immune deficiency diseases. An extensive science base would be created of special importance to studies of toxicology and the effects of environmental contaminants; and we would hasten the day when physicians may be able to repair or replace defective genes.

Sentiment in the scientific community at this time favors approaching this massive project through a carefully planned stepwise effort rather than a mass attack. In preparation for

further efforts on the project, we are developing collaborative arrangements with the scientific communities in Europe and Japan, and cooperating with other Federal agencies having interest.

The Administration proposes a long term policy of stable and sustainable support for the NIH. The President's budget seeks $5.8 billion in obligational authority in FY 1987 and 1988. The Administration also proposes a policy of appropriating the total NIH allowance for research project grant commitments at the time that they are incurred.

The key adjustment proposed for FY 1987 by the Administration is to extend the availability of $334 million of FY 1987 funds so that they could be obligated during FY 1988. The proposed carryover would be achieved by awarding 700 of the FY 1987 estimated 6,394 competing research project grants in FY 1988 rather than the current fiscal year, and by reducing the average cost of both competing and noncompeting awards in FY 1987. You may be assured, however, that we are now awarding grants in a manner consistent with the funding levels contained in the FY 1987 appropriation. Should Congress enact this proposal of extended availability, only those projects scheduled to receive awards subsequent to congressional action would have their grants reduced.

The revised budget for FY 1987, that would result from the proposed changes, would fund approximately 19,111 total research project grants, an increase of about 315 from the FY 1986 comparable level. All other NIH mechanisms would be funded in the same amounts as in the original FY 1987 appropriations. This includes funding for 560 centers, an increase of 23 over FY 1986, and 10,867 full-time research trainees, an increase of 485 over FY 1986. The funding for AIDS research, would not be affected by the Administration's proposal to revise the FY 1987 budget.

The President's budget request for FY 1988 includes $5,534 million in new budget authority. With the extended availability of $334 million in FY 1987 funds, the total obligational authority for 1988 would be $5,869 million, which is approximately equal to the level of the revised 1987 budget. The request would support 19,131 total research project grants, about the same number as in the proposal for the current year. New and competing renewal grants under the President's FY 1988 proposal would number 5,709 as compared with 5,654 in the revised 1987 budget, and 6,211 in 1986. The average cost per grant would be about the same as in 1987, $164,000 per award.

The 1988 request for research training, $233 million, would support approximately 10,867 trainees, the same number as in the revised 1987 level--approximately the number recommended by the National Academy of Sciences.

The number of research centers would be the same in 1988 as in 1987, but with a decrease in funding support of $1.4 million from FY '87 to the new figure of $522 million.

In the aggregate, the other NIH research mechanisms, such as other research grants, research contracts, the intramural research

programs, research management and support, and disease control, would be maintained at approximately their FY 1987 comparable funding levels. Two exceptions are the Biomedical Research Support Grant (BRSG) and the Extramural Construction Program; both of which are proposed for elimination in 1988. Because of the continuing interest in investigator-initiated research project grants as the most appropriate form of support and the growing concern over budget constraints, the BRSG program and the Extramural Construction Program must rank as lower priorities when compared with other NIH programs.

As part of the President's biomedical research stability policy, the FY 1988 budget also includes a request for advanced appropriations in the amount of $2,726 million to support the outyear commitments (FY 1989 through 1994) generated by the award of competing research project grants during FY 1988. This approach to grant funding would focus attention on the total project and inform the research community of the total funds available for continuation costs. Provisions are made for modest annual increases of the average costs per grant. The funds for the noncompeting continuations would be awarded on an annual basis, as they are now.

I would be pleased to respond to questions about the budget or other matters pertaining to NIH.

INTRODUCTORY REMARKS*

by

William F. Raub, Ph.D.**

Good evening ladies and gentlemen and welcome to the annual R. E. Dyer Lecture. I am Bill Raub, Deputy Director of NIH, and am here to greet you on behalf of our Director, James B. Wyngaarden. This series of lectures was established in 1950 to pay tribute to the late Dr. Rolla Eugene Dyer upon his retirement as Director of the National Institutes of Health.

In 1916, at the beginning of Dr. Dyer's career in the Public Health Service, he was assigned to do bubonic plague field studies in New Orleans. Five years later, he came to Washington to work with the Hygienic Laboratory, which was to become the National Institute of Health. In 1936, he was appointed Chief of NIH's Division of Infectious Diseases, the forerunner of the National Institute of Allergy and Infectious Diseases.

Early in his research career, Dr. Dyer made significant contributions in combatting endemic typhus. He not only showed how it was spread but also helped to develop a vaccine. Moreover, his work with scarlet fever, influenza, Rocky Mountain spotted fever, and Q fever resulted in important medical and epidemiologic findings.

Later, as Director of NIH, Dr. Dyer coupled his scientific knowledge with his astute administrative insight and led NIH into a period of intense expansion. Under his leadership, NIH took important steps toward becoming what it is today.

In recognition of Dr. Dyer's contributions to NIH, the selection of speaker for the Dyer lecture series is made personally by the Director of NIH with the advice of his senior scientific staff. Scientists are chosen for this honor as an acknowledgement of their recent contributions to medical research, particularly in the field of infectious diseases.

Tonight's speaker, Dr. Bernard N. Fields, is indeed worthy of this tribute. His research in viral pathogenesis has brought profound insights to the science on a molecular level. Recognizing the value of the reovirus as a model virus system, with its double-stranded RNA and segmented genome, Dr. Fields has been able to unravel the structure and function of specific genes of the virus. He has shown how these genes, along with other fundamental features of viruses, are involved in viral pathogenic mechanisms.

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*For Dr. Bernard N. Fields at the R. E. Dyer Lecture on March 11, 1987, in Masur Auditorium.

**Deputy Director, National Institutes of Health, Bethesda, Maryland.

Furthermore, Dr. Fields has been a source of inspiration to the young scientists with whom he has worked. Under his tutelage, many have gone on to make signficant research contributions in their own right.

Dr. Fields did his undergraduate work at Brandeis University and, in 1962, received his medical degree from New York University School of Medicine. Both his internship and residency were served at Beth Israel Hospital in Boston. After a clinical and research fellowship at Harvard Medical School, he accepted a fellowship at Albert Einstein College of Medicine and subsequently joined Einstein's Departments of Medicine and Cell Biology.

Dr. Fields was awarded an honorary A.M. degree by Harvard University in 1976 and is a member of many professional societies, including the American Society for Clinical Investigation and the Association of American Physicians. He has served on numerous editorial boards, panels, study sections, and committees. Recently, he was elected to the National Academy of Sciences. Other honors accorded him include the American Society for Microbiology Wellcome Lectureship and the Thayer Lectureship at The Johns Hopkins University School of Medicine.

Dr. Fields, who has been at Harvard Medical School since 1975, is now the Adele H. Lehman Professor of Microbiology and Molecular Genetics. His lecture tonight is titled "The Molecular Basis of Viral Virulence."

Dr. Fields.

STATEMENT BY

JAMES B. WYNGAARDEN
DIRECTOR

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

U. S. SENATE SPECIAL COMMITTEE ON AGING

MARCH 13, 1987

Mr. Chairman and members of the Committee, I am Dr. James B. Wyngaarden, Director of the National Institutes of Health (NIH). I am responding to your invitation to present testimony on the impact of the President's fiscal year 1988 budget request on NIH programs affecting the elderly.

The NIH is the principle biomedical research agency of the Federal Government. The NIH supports biomedical and behavioral research in this country and abroad, conducts research in its own laboratories, trains promising young researchers, and promotes the acquisition and distribution of medical knowledge. These research activities uncover new ways to prevent and ameliorate disease and disability, seek to lessen the enormous economic and human toll exacted from the Nation, and lead to better health care for all Americans.

The National Institute on Aging (NIA), consistent with its Congressional charter, supports and conducts biomedical and behavioral research and training on the aging process and the common problems of older people. NIA-supported investigators are studying a wide range of topics relevant to this mission. Among these topics is the continued effort to differentiate between normal aging and those disease states and conditions common to older people which are potentially preventable or reversible.

The NIA supports a broad spectrum of research and training aimed at easing or eliminating the physical, psychological and social problems that beset many older persons. Research efforts include studies on the etiology, diagnosis and treatment of Alzheimer's disease; factors such as risks of falls, osteoporosis and osteoarthritis which contribute in major ways to

immobility and hip fractures; the common problem of urinary incontinence; and the development of better understanding of nutrition, exercise, and healthy behaviors in maintaining health and functioning in later years.

NIA Intramural research activities include its 29-year-old Baltimore Longitudinal Study of normal aging, a research program in dementia in the NIH Clinical Center in Bethesda, and four Established Populations for Epidemiological Studies of the Elderly. The Institute also supports 10 Congressionally-mandated Alzheimer's Disease Research Centers, six Alzheimer's disease case registry programs, and a number of cell culture and small animal resources for research scientists studying the aging process throughout the nation.

NIA research is complemented by the research of at least four other institutes at the NIH: the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS); the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); and the National Eye Institute (NEI). These institutes support research in such areas as Alzheimer disease, systolic hypertension, osteoporosis, osteoarthritis, glaucoma, and cataracts.

ALZHEIMER'S DISEASE

NIA-supported research has recently produced a number of important discoveries and advances, particularly in the efforts to understand and conquer Alzheimer's disease. In just the past few weeks scientists supported primarily by NIA, as well as other Institutes at NIH, have

reported fundamental advances in understanding genetic origins of at least some instances of Alzheimer's disease and the genetic region responsible for producing one of the principal proteins in the brain lesions in this disease.

In four families, residing in several countries, in which Alzheimer's disease is highly and predictably inherited, these scientists have used modern molecular genetics techniques to determine that the genetic basis for their disease is contained in a small section of chromosome 21 - one of the 23 pairs of human chromosomes. In other important related advances, another NIA grantee has isolated and analyzed an abnormal protein, the "A68" protein, from the brains of Alzheimer's disease patients that appears to be specific for Alzheimer's disease. This protein may prove to be a biochemical indicator of the disease, since it can be detected in spinal fluid. The NIA is supporting further efforts to identify and genetically characterize afflicted families, bank cells derived from family members, isolate cellular DNA and coordinate Restriction Fragment Length Polymorphism linkage studies utilizing these DNA samples.

Virtually simultaneously, several groups of scientists have reported cloning the genetic area which controlls the production of the amyloid protein that is deposited in the lesions in the brains of Alzheimer's victims. NINCDS researchers have cloned a normal human gene involved in making this amyloid. The gene directs cells to manufacture a large protein involved in the formation of amyloid, the abnormal substance seen as patches of degenerating brain tissue in Alzheimer's patients, as well as in the brains of normal older adults. This finding represents an important

clue in understanding the cause of Alzheimer's disease and provides the basis for further research that may one day lead to the prevention and treatment of this and other progressively deteriorating disorders. It appears that this gene is also located on human chromosome 21, the chromosome associated with Down's syndrome. Of additional interest is the finding that adult Down's patients have Alzheimer's disease-like plaques and tangles in their brains.

In addition to the research outlined above, NINCDS scientists interested in neurological dysfunctions affecting older people are using a synthetic drug called MPTP to gain new insights into the cause of Parkinson's disease and are exploring ways to cope with hearing loss through studies concerning the mechanisms by which sound is transmitted to the brain. Potentially important applications to Alzheimer's disease and Parkinson's disease may also emerge from current studies of neuronal implantation. NINCDS scientists have implanted cortical cells from young rats into the brains of aging rats enabling them to remember how to solve life threatening problems by methods they previously knew but have lost the ability to remember. This research may someday not only provide possible approaches for treating patients with Alzheimer's disease, but for reversing memory deficits that result from the normal processes of aging.

A new initiative which NIA plans to begin fiscal year, in cooperation with the Alzheimer's Disease and Related Disorders Association (ADRDA), is a multicenter clinical trial of the efficacy of tetrahydroaminoacridine (THA) as a potential drug to slow the progression of Alzheimer's disease and improve the level of functioning of Alzheimer's disease patients. The need

for an adequate controlled clinical trial is based upon some positive and provocative data, published in 1986, that indicate considerable improvement in function in a small number of Azlheimer's victims treated with THA. This paper engendered predictable excitement and dictated the need for a careful investigation to determine (1) if THA is efficacious in Alzheimer's disease; (2) the proportion of patients, and their characteristics, that obtain a clinically meaningful improvement from THA; and (3) the degree of improvement that can be anticipated. The Food and Drug Administration is working closely with NIA in guiding the further evaluation of this drug, in order to assure as quick an answer as possible on its safety and efficacy.

STROKE

The NINCDS supports individual investigators and teams of scientists in stroke and positron emission tomography (PET) research centers. Studies that monitor populations of stroke patients over periods of years give scientists time perspective to evaluate long-term damage and treatment effectiveness. The result of the extracranial/intracranial bypass surgery study, which indicated that [illegible]e surgery is of no therapeutic benefit, has prompted scientists to con[illegible]r similar evaluations of other commonly used neurosurgical and vascular surgical procedures, such as endarterectomy - the surgical removal of the inner layer of an artery when thickened or occluded, as by inner plaques. Such research is important to the health and pocketbooks of older Americans. Research continues to build toward the goals of stroke prevention, recovery of brain function, and improved quality of life for those who suffer stroke, all important concerns as our population ages.

SYSTOLIC HYPERTENSION

It has been estimated that in the United States alone, more than three million persons over the age of 60 have isolated systolic hypertension (systolic blood pressure over 160 mm Hg, diastolic blood pressure under 90 mm Hg) on a single measurement, and approximately half of them have systolic blood pressure elevation on repeated examinations. These persons face an excess risk of stroke, other cardiovascular disease and death. Systolic hypertension may even play a part in the etiology of multi-infarct dementia. A study on Systolic Hypertension in the Elderly, co-sponsored by the NIA and the NHLBI, has been developed to look at this population with sustained isolated systolic hypertension (ISH). This study is a multicenter clinical trial designed to determine whether the long-term administration of antihypertensive therapy for the treatment of isolated systolic hypertension, in men and women over the age of 60, reduces the combined incidence of fatal and nonfatal stroke. In addition, the study will include an evaluation of the effect of long-term antihypertensive therapy on cardiovascular morbidity and mortality in older persons with ISH, possible adverse effects of chronic use of antihypertensive drug treatment in this population, and the effect of therapy on indices of quality of life.

OSTEOPOROSIS

Another important area of research supported by NIA concerns risk factors for hip fractures. Osteoporosis significantly increases the risk of hip fracture. Although there is general agreement that estrogen therapy will slow bone loss in post-menopausal women, there remain many unanswered questions, including the exact mechanism of action, the best method of

administration, the risks of prolonged use (which may be influenced by the route of administration) and the effects in women who are many years post-menopausal.

Scientists at the NIA Gerontology Research Center in Baltimore have devised what may be highly effective and safe procedures for taking hormone medication such as estrogen. Administration of these drugs under the tongue may enhance the success of treating such conditions as osteoporosis, premenstrual syndrome, and hypopituitarism. Other routes for administration of hormone medications which these scientists have helped develop are transdermal patches and nasal sprays. Such methods may prove superior to conventional ways of taking such medication.

The new National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has targeted osteoporosis for special research emphasis in many ways, including a recent Scientific Workshop on Osteoporosis co-sponsored with other NIH Institutes, a program announcement focusing on "Research on Bone Active Hormones and Cytokines," and a Request for Applications for Programs of Excellence of Research on Osteoporosis jointly issued by the NIA, NIAMS, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The Programs of Excellence will focus on basic mechanisms leading to abnormal bone metabolism, means for accurate assessment of quantity and quality of bone; epidemiology and determining risk factors, preventive measures for various age groups, and treatments to restore structurally competent bone to the skeleton. A new clinical trial beginning in FY 1987 will be co-sponsored by NIAMS, NIA, NIDDK, NHLBI, and the National Institute of Child Health and Human

Development (NICHD). This trial will investigate the effects of estrogen and progestin on a variety of outcomes, including lipoproteins, bone mass, and gallstone formation.

OSTEOARTHRITIS

Proceedings and recommendations have been recently published from a very successful scientific workshop co-sponsored by NIAMS and NIA on Etiopathogenesis of Osteoarthritis. Workshop participants included experts in epidemiology, anatomy and pathology, biochemistry, bioengineering, inflammation, and clinical medicine. More than 120 recommendations for research areas to be pursued emerged from the workshop. A program announcement is being prepared by the NIAMS and NIA to stimulate research on osteoarthritis in these targeted areas.

DISEASES OF THE EYE

Ocular disorders that are common in older adults and are actively being studied by the NEI include aging-related maculopathy, cataract, and glaucoma. Aging-related maculopathy selectively affects the macula, the small area of the retina that provides sharp central vision. It occurs primarily with aging, impairing to some degree the vision of millions of Americans over age 50. An NEI-supported clinical trial, the Macular Photocoagulation Study, provided the first conclusive evidence that the vast majority of cases of blindness resulting from this disease could be prevented or delayed significantly by timely laser treatment if the disease is recognized early.

The NEI devotes most of its funding in the cataract program to research aimed at developing means of preventing or slowing the development of cataract or of treating it nonsurgically. Investigations are currently under way employing molecular biological techniques to study the alteration of lens proteins and investigate the extent to which such alteration affects transparency. Previous studies have indicated that oxidation of protein and lipid components of the lens is related to the onset of senile cataract. Investigators are attempting to determine whether a prime factor leading to this oxidative damage is the ambient ultraviolet light radiation in sunlight. Attempts are also being made to prevent or arrest cataract in animal models using antioxidants. Various epidemiologic studies of cataract are under way to determine environmental, nutritional, and genetic factors that may be involved in cataract development.

Although glaucoma may occur at any time in life, the risk of developing glaucoma increases with age. Treatment for glaucoma, whether by drugs or surgery, is aimed either at diminishing aqueous humor production or at facilitating its outflow. In an attempt to improve the outcome of glaucoma surgery, the compound 5-fluorouracil, a chemical that inhibits cell proliferation, is being administerated postoperatively under the conjunctiva of the eye in a randomized clinical trial. Administration of this chemical has been shown to enhance the success of conventional glaucoma surgery in high-risk patients. The purpose of the trial is to define further the safety and efficacy of this treatment. Another NEI-supported clinical trial is comparing the safety and efficacy of argon laser trabeculoplasty with that of traditional medical treatment with topical drugs in newly diagnosed patients with primary open-angle glaucoma.

ORAL HEALTH

Improving the oral health of older people is the focus of a collaborative project between the NIA, the National Institute of Dental Research (NIDR) and the Veterans Administration. A research agenda has identified critical areas such as the relationships between oral health and nutritional status and chronic pain in older persons.

GERIATRIC TRAINING

In response to the 1984 Congressionally-mandated plan to improve and expand training in geriatrics and gerontology, the NIA has intensified its efforts to train investigators and educators in aging research. This is being accomplished through the design and implementation of a variety of new approaches to training and career development. The Geriatric Leadership Academic Award, the Complementary Training Award for Research on Aging, and the Co-Funded Institutional National Research Service Award were first made in FY 1985. Other approaches include summer institutes in geriatric research for medical students and post-doctoral trainees, Special Emphasis Research Career Awards, and a training component in the NIA Teaching Nursing Home Awards.

In addition, as authorized by Congress in the 1986 Omnibus Health Act (P.L. 99-660), NIA is this year initiating a Program for Leadership and Excellence in Alzheimer's Disease, which also includes a training component, and is developing an Alzheimer's Disease Information and Education Center to provide health professionals and the public with up-to-date information on all aspects of this disease.

INTERAGENCY COMMITTEE

The Interagency Committee on Research on Aging, chaired by the National Institute on Aging, NIH, provides a central focus for Federal research on aging. Its key functions include: identification of research needs as well as research interests that cut across Federal agencies and departments in order to promote appropriate collaboration and to avoid duplication of effort; sharing of proposed research strategies and anticipated projects; and exchange of information about existing research. Other interests of the Committee include looking into the feasibility of developing a computerized database of information on federally-supported research on aging and convening a group of agency representatives interested in activities to improve the quality of home care of older adults.

The process of development of the President's budget is a lengthy one, encompassing well over half a year and numerous clearances and adjustments. Priorities that emerge represent a series of choices and compromises. Each institute at NIH must, by the nature of the process, have its priorities compete with those of the other institutes, all within the context of the overall requirements of the President's budget. These NIH priorities then compete with those of other agencies within the Department. To the extent possible, NIH and the Department have emphasized research related to aging, and most particularly research on Alzheimer's disease.

With regard to the impact of the proposed FY 1988 budget, the NIH budget request includes $5,534 million in new budget authority. With the extended availability of $334 million in FY 1987 funds, the total obligational

authority for 1988 would be $5,869 million, which is approximately equal to the level of the revised 1987 budget.

This budget, in addition to maintaining approximately the same number of research project grants at a constant level, would also permit the NIH to continue to fund the same number of center grants, including the Alzheimer's Disease Research Centers, but with a decrease in funding of $1.4 million from the 1987 level to a new figure of $522 million. Support for career awards and research training would be available at almost the same level as the 1987 revised budget, with the training program supporting approximately 10,867 trainees - almost the level recommended by the National Academy of Sciences. In the aggregate, the other NIH research mechanisms would be maintained at a level almost commensurate with comparable 1987 funding levels. Under the President's budget we can expect to see continued advances in understanding the biological basis of aging, and we will certainly continue our remarkable progress in Alzheimer's disease.

Mr. Chairman, this concludes my prepared statement. I will be glad to answer any questions you or the members of your Committee may have.

FASEB AND NIH: A PARTNERSHIP FOR RESEARCH*

by

James B. Wyngaarden, M.D.**

- Congratulations to FASEB on its 75th anniversary, founded in 1912 to facilitate communication between sciences (biology and medicine) and individual scientists.

- Coincidentally, NIH's 100th anniversary.

- Both organizations have roles to play in finding solutions to the great unsolved medical mysteries through the further acquisition of new fundamental knowledge.

- Most members of NIH, and extramural scientists supported by NIH are members of one or more of the constituent societies of FASEB.

- Therefore it is no mystery that our goals show such extensive overlap as to be virtually synonymous.

- My personal association with FASEB goes back to 1947, when as a junior medical student at the University of Michigan, I presented my first scientific paper before the American Society of Pharmacology and Experimental Therapeutics. I had worked during two summers and elective time in Maurice Seevers' department and it was also through him that I met Dr. K. K. Chen at that meeting.

- My association with Dr. Hitching, whom we also honor today, is more recent, but also more intimate because we shared interests in these elixirs of life, purines and pyrimidines. And also because for about twenty years we were neighbors in N.C.

- Unfortunately, my paths and those of Milton Lee did not cross in any personal way to my knowledge.

- But let me return to my central theme, the interrelatedness of our two great institutions. I have already commented about the congruence of our goals. I should go further--the NIH is utterly dependent upon the members of FASEB to achieve its goals and to pursue its mission, which as simply stated in the Public Health Act of 1944, is to uncover new knowledge of potential benefit to the health of the American people. The activities toward this goal are conducted by people, and the majority of these people are members of FASEB. These are the men and women who devote themselves, often their entire lifetimes, to biological research.

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*Presented at the Dedication of the New Wings of the Milton Lee Building and FASEB Conference Center, March 29, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

- Research has been called "play, carried into adult life." Perhaps, because it is endlessly fascinating and captivating, it is difficult to regard it as work.

- Medical research is also a form of national defense -- an endless struggle against implaccable enemies. It pains me that the quest for NIH grant support should be so fiercely competitive and that our resources, though vast, cannot support a larger share of the meritorious work that is proposed. We are unable to capitalize fully on our immense potential. We are wasting a part of a precious national resource: the trained, creative investigator.

- The brief examples of the strategy of a predominantly categorical organization of scientific research in the life sciences have brought the U.S. to its position of world leadership in this field.

  A) Biotechnology
  B) Alzheimer's Disease
  C) AIDS

Biotechnology

1) Genetics -- 1950's
2) Recombinant DNA/Immunology
3) Biotechnology Industry
4) New insights -- pervasive
5) Sequencing the human genome

Alzheimer's

1) Dr. Caleb Finch of the University of California said, "I would not be surprised if the major new resources required for a serious attack on Alzheimer's disease do not also benefit the basic neurosciences on the same scale as funding for cancer research has done for many areas of molecular, cell, or developmental biology."

2) Chromosomes 21
   2 Alzheimer's
   1 Down's

AIDS

1) Remarkable progress in 5-6 years.
2) Rests on fundamental research of earlier decade:
   a) Virology
   b) Molecular biology - reverse transcriptase
      restrictive endonucleases
      T-cell growth factor
   c) Vaccine strategies

- In closing, let me say how pleased I am to be here to help FASEB celebrate its 75th anniversary. Congratulations. I hope that 25 years from now, in 2012, the Director of the National Institutes of Health will again be here to promote our continuing partnership in advancing fundamental biochemical knowledge. Thank you.

TOWARD A NEW SYNTHESIS IN MEDICINE*

by

James B. Wyngaarden, M.D.**

- I am honored to have been asked to join the distinguished representatives of the United Kingdom, France, and the Federal Republic of Germany in congratulating the American Physiological Society (APS) on the occasion of its 100th anniversary. Inasmuch as the National Institutes of Health (NIH) is not yet a sovereign state, I must assume that I have been accorded this honor because the institution I represent is also observing its 100th bithday.

- Both the NIH and the APS owe much to European science of the 19th century.

  At that time, and for most of its history, medicine had been anything but scientific, being dominated by empiricism and shackled by dogma. Medical practices had been primitive, often more harmful than helpful--bleeding, infusion of metals, strange extracts, nostrums and diets--that had no scientific foundation. Not surprising.

  Change came slowly, but grew out of an increasing application of scientific methodology and the new principles of physics and chemistry, to which in the late 1800's were added bacteriology, pathology, and physiology.

  Koch and Pasteur in vanguard identified microorganisms with specific diseases--anthrax, tuberculosis, pneumococcus, streptococcus. They were a major influence on Dr. Joseph Kinyoun, the first Director of the Laboratory of Hygiene at the Marine Hospital Service facility on Staten Island, New York, progenitor of the NIH, who spent some time in training in their laboratories in Berlin and Paris.

- Claude Bernard, a major figure in science, and the foremost physiologist of his day, started as a French playwright. He was both a scientist and a philosopher of science, noted for discovering that the liver converts sugar to glycogen and stores it. He clarified operation of the vasomotor system and of the action of curare on the nervous system. He proposed the concept of the "milieu interieur." This led to the belief that the relative independence of warm blooded animals from exterior influences owes to their ability to maintain a relative constancy of the internal environment. And this gave rise to additional concepts of the body as a series of self regulating or homeostatic systems. These concepts gave shape and substance to the field of physiology for the next century. One of his most enduring concepts was the experimental method of observation as a basis for progress.

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*Presented to the American Physiological Society Open Plenary, Washington, D.C., March 29, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

- At about the time the APS was founded, the NIH also had its humble beginnings. Medicine took up residence in the laboratory as well as at the bedside, and its progress in the years since that time has been made possible and nurtured by increasing understanding of the fundamental structures and mechanisms of living organisms.

- From the physiologist's perspective came understanding of the unifying principles--the interplay of mechanisms--the functioning of organ systems--the integrated whole. More recently, there has been a parallel thrust towards a reductionist approach. Details, D^2, until minute structures and isolated molecular mechanisms are laid out for understanding.

- From such studies we have seen science define the composition of organs, tissues, membrances, and cells. We understand the biosynthesis of hundreds of compounds in the body. The regulation of body processes has been minutely described, and pharmacologic agents are understood in terms of mechanism.

- At the molecular level we today understand 200 inborn errors in terms of specific missing or abnormal enzymes or proteins; 240 abnormal hemoglobins can be described, and for each a specific defect in DNA can be identified.

- One of the fields that is making very rapid progress in terms of understanding the biological progress at the level of the tissue and cell is neurology. Particularly stunning are the new insights we have gained into the plasticity of the nervous system.

- There has been a confluence of disciplines. Anatomy, physiology, pharmacology, biochemistry, bacteriology, and pathology are expressed in the common language of chemistry. The next wave will be genetics, molecular biology, physiology, chemistry, structural biology to describe atomic details. Examples of some of these are viruses, complex proteins, nucleic acids, and brain lipids in a three-dimensional array, assigning specific functions to specific minute regions of the complex structures.

- Counter reductionism has led to hybrid disciplines such as immunogenetics, pharmocogenetics, neurophysiology, physiological psychology, and a host of others. What is needed are synthetic concepts and interrelationships, coordination, regulation, and communication. These are the challenges of 20th and 21st century physiology -- the unification of these seemingly disparate disciplines and observations of the life sciences.

- I often think that the founding members of the Nobel Prize Committee, sometime just before 1901, had instincts and wisdom not unlike those of the authors of our Constitution. They too drafted a timeless document in the life sciences. The Prize is for Physiology or Medicine. They must have foreseen that no matter how reductionistic the subject matter of the Prize, it is in its relationship to the whole that it achieves its true significance.

- On behalf of the 14,000 members of the NIH, and indeed on behalf of the more than 50,000 scientists whose work we support, I salute the American Physiological Society on its 100th anniversary. Thank you.

TALKING POINTS*

by

James B. Wyngaarden, M.D.**

- o As you may know, last October the National Institutes of Health began what is to be a year-long observance of its 100th anniversary.
  - Planned for this period are seminars, conferences, symposia, receptions, dinners, television broadcasts, an NIH alumni reunion, and a variety of events here and in many locations across the United States and in other countries, providing public recognition of the role of the NIH in what is being described as "A Century of Science for Health."
- o The American Physiological Society (APS) is also celebrating its 100th anniversary, and, as part of its centennial celebration, has dedicated this week of scientific meetings, plenary sessions, exhibitions, and special events to commemorate the occasion.
- o In keeping with this joint celebration, it is a pleasure for the NIH to join with the APS in sponsoring this symposium today marking "The Second Century of Experimental Biology."
- o Over the last few decades, as science became more sophisticated and began focusing on problems of increasing complexity, more reductionistic trends led to greater collaboration between scientists from various disciplines. This movement toward mutlidisciplinary research has fostered communication between scientific disciplines and has provided approaches to research problems that earlier had remained intractable. During this period, we have seen many examples of how new knowledge gained in one field has been applied successfully to the solution of problems in entirely different fields of study.
- o One example: in structural biology where great strides in x-ray crystallography, biophysics, molecular modeling, and computer graphics have contributed new insights concerning the molecular structure of proteins, the principles governing the arrangement of atoms within a molecule, and the development of methods to modify the structure of molecules to achieve new desired properties.
- o Among other things, these developments have enormous implications for the construction of a sound rationale to guide the future design of targeted antiviral drugs that can bind to specific regions of target macromolecules.

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*For the Opening of the NIH/APS Symposium at the American Physiological Society Annual Meeting, Washington, D.C., on March 31, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

- In fact, to capitalize on this opportunity, the NIH has initiated a new Targeted Antiviral Drug Program designed to focus and intensify activities directed toward the incorporation of the growing body of knowledge in structural biology into approaches to the design of antiviral drugs against the AIDS virus (but with general applications).

- The program will have two major components, one intramural and the other extramural component:

  - The intramural component is intended to mobilize and deploy the vast array of relevant scientific talent that is found in the various laboratories of the NIH to better focus on the biology and fine structure of viruses and the development of specific drugs that inhibit viral attachment, penetration, replication, integration, and expression.

  - A similar extramural counterpart will be established that will also draw in superb science from allied fields. This will be done through the support of several multidisciplinary research groups that will be centered around the theme of the application of structural biology to the development of targeted antiviral drugs. These research groups will also provide training for graduate students and postdoctoral scientists.

  - Informal interactions and exchanges of information among all the groups in the program is expected, and an annual conference of intramural and extramural participants is planned.

- It is also clear that the desire and necessity to approach complex research problems from a variety of perspectives has led to arrangements which extend beyond multidisciplinary research and, in fact, have resulted in the merger of traditional disciplines into new "hybrid" disciplines whose names better reflect the true interests and activities of their pactitioners. We have seen, for example, the proliferation of such interest areas as immunogenetics, neurobiology, structural biology, pharmacogenetics, and a host of others.

- But this merger of traditional disciplines goes beyond mere contractions of names. The blending of disciplines into novel research approaches has had dramatic results in terms of research accomplishments.

- An example which comes from work unambiguously centered in your discipline--physiology--comes to mind. Research on the role of atrial natriuretic factor (ANF) in the control of blood pressure has been advanced significantly as a result of the confluence of several major streams of research.

  - In the 1950s, histologists noted the presence of granular deposits in the atria of both humans and experimental animals.

  - It was not until 1964, however, that studies were published on the morphological characterization of specific atrial granules.

- Although it was earlier postulated that the atria were involved in extracellular volume regulation, it was not until 1981 that experiments showed that the atria of mammals did indeed contain a natriuretic factor.

- Between 1981 and the present, there has been a virtual explosion of activity in which studies employing recombinant DNA techniques, monoclonal antibody technology, protein microsequencing, and x-ray crystallography have resulted in the cloning of the gene responsible for the synthesis of ANF, the determination of the amino acid sequence of the ANF precursor, and the identification and sequencing of a variety of smaller active peptides.

  -- The ability to clone the gene and synthesize it in quantity has eliminated the need for working with large numbers of mammalian atria. This has spurred additional structure-activity studies directed toward understanding the effect of ANF on the kidneys, smooth muscle, and on the renin-angiotension-aldosterone system.

  -- In 1984, radioimmunoassays were developed that are capable of detecting the presence of ANF in the plasma and measuring the changes in the levels of ANF after experimental manipulations.

- These developments now permit a direct assault on such questions as:

  -- Which of the isolated peptides are naturally occurring?

  -- What are the stimuli for the biosynthesis of ANF precursor?

  -- What are the stimuli and mechanisms for the biochemical processing of the ANF precursor? and

  -- What are the cellular and molecular mechanisms for the secretion of atrial peptide?

- When this information is obtained, we will have a much better understanding of the role played by ANF in sodium balance, blood volume, and blood pressure homeostasis, and whether or not ANF is a factor in the pathogenesis of a variety of cardiovascular diseases, including hypertension.

o I believe this trend toward the coalescence of traditional scientific disciplines will accelerate and intensify as we continue to achieve a greater depth of experimental approach.

o The purpose of this symposium is to assist in establishing a dialogue between physiologists and scientists in fundamental, underlying areas of science with the goal of exploring this trend that has been occurring toward the confluence of many discrete biomedical sciences. It offers a fine platform for addressing the interdependence of reductionist and integrative science.

- To accomplish this goal, we have structured a panel discussion around the central theme that recent developments in such areas as molecular biology, genetics, immunology, and neurobiology have underscored and accelerated this trend. We wish to demonstrate the fact that as new and powerful tools and techniques emerge, and as new knowledge is developed concerning the fundamental molecular and chemical levels of biological organization, we are rapidly approaching the emergence of a universal language governing further inquiry. This trend will have important implications for all branches of science, including physiology.

o We have been very fortunate in assembling a panel of individuals with expertise in areas of science outside of physiology as well as members who are currently incorporating the concepts and tools of these other sciences into their physiological research. Through presentations and discussion, we hope to demonstrate the potential influence of current trends on the future course of physiological research.

A SECOND CENTURY OF SCIENCE FOR HEALTH*

BY

JAMES B. WYNGAARDEN, M.D.**

DURING THE PAST WEEKEND IT HAS BEEN MY PLEASURE TO PARTICIPATE IN THE DIAMOND ANNIVERSARY CELEBRATION OF FASEB AND TO SPEAK AT THE OPENING OF THE CENTENNIAL SESSION OF THE AMERICAN PHYSIOLOGICAL SOCIETY. IN BOTH OF THESE EVENTS I WAS DELIGHTED THAT RECOGNITION WAS ALSO GIVEN TO THE CENTENNIAL OF THE NATIONAL INSTITUTES OF HEALTH. THE NIH CENTENNIAL IS BEING OBSERVED IN A YEAR-LONG SERIES OF EVENTS HERE AND ABROAD THAT BEGAN LAST OCTOBER AND WILL CULMINATE IN A GALA CELEBRATION, AND SYMPOSIA, AN OPEN HOUSE, AND AN ALUMNI REUNION IN MID-OCTOBER THIS YEAR HERE IN WASHINGTON.

ALTHOUGH THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS (ASPET) IS NOT COMMEMORATING A "PRIME" ANNIVERSARY THIS YEAR (HAVING BEEN ESTABLISHED IN 1908), IT WAS ONE OF THE THREE FOUNDING SOCIETIES OF FASEB (TOGETHER WITH THE AMERICAN PHYSIOLOGICAL SOCIETY AND THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS) AND THUS RIGHTFULLY CAN JOIN AS A FULL PARTNER IN CELEBRATING FASEB'S SEVENTY-FIFTH ANNIVERSARY.

INASMUCH AS MY FIRST RESEARCH WAS IN THE REALM OF PHARMACOLOGY, THE RECENT SPECTACULAR ADVANCES IN PHARMACOLOGY ARE ESPECIALLY EXCITING TO ME. IN WHAT SEEMS A VERY SHORT TIME, THIS DISCIPLINE HAS MOVED INTO A NEW ERA.

OVER THE CENTURIES, AND IN FACT UNTIL VERY RECENTLY, DRUGS HAVE BEEN DISCOVERED IN LARGELY A HIT-OR-MISS FASHION. BECAUSE THEY MAY HAVE BEEN OBSERVED TO BE EFFECTIVE IN THE TREATMENT OF DISEASE, MANY COMPOUNDS HAVE BEEN ACCEPTED AS DRUGS DESPITE THEIR SOMETIMES SERIOUS SIDE EFFECTS. IT IS ONLY IN THE PAST FEW YEARS THAT NEW ANALYTICAL TECHNIQUES AND COMPUTER PROGRAMS HAVE MADE IT POSSIBLE TO DESIGN NEW OR IMPROVED DRUGS WITH FEWER SIDE-EFFECTS AND, IN MANY INSTANCES HAVING ENHANCED PHARMACEUTICAL ACTIVITY.

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**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

THE STORY OF CIMETIDINE, WITH WHICH MANY OF YOU ARE FAMILIAR, IS AN ILLUSTRATION OF THE KINDS OF STRATEGIES AND TECHNIQUES REQUIRED FOR THE DEVELOPMENT OF A DRUG TAILOR-MADE FOR A SPECIFIC PURPOSE. IN THIS INSTANCE THE PURPOSE WAS TO MAKE A TOTALLY NEW TYPE OF DRUG THAT WOULD PREVENT PEPTIC ULCERS.

IT HAD LONG BEEN KNOWN THAT HISTAMINE IS PRESENT IN LARGE AMOUNTS IN THE GASTRIC JUICE OF ULCER PATIENTS AND IS A POTENT STIMULUS OF ACID PASDUCTION. ON THE BASIS OF SUCCESSFUL TREATMENT OF ALLERGIC REACTIONS WITH ANTIHISTAMINES, IT WAS POSTULATED THAT A SIMILAR APPROACH WOULD WORK IN THE GI TRACT, BUT THE CLASSIC ANTIHISTAMINES (DESIGNATED AS H^1 BLOCKING AGENTS) WERE INEFFECTIVE AGAINST GASTRIC ACID SECRETION. FROM THIS FACT IT WAS ASSUMED THAT THERE WERE TWO DIFFERENT HISTAMINE RECEPTORS ON CELL SURFACES. A TEAM LED BY SIR JAMES BLACK THEN INTENSIFIED ITS SEARCH FOR AN ANTAGONIST THAT WOULD BLOCK HISTAMINE AT A SECOND RECEPTOR SITE IN THE ACID SECRETING CELLS OF THE STOMACH, IF, IN FACT, AN H_2 RECEPTOR SITE EXISTED. SOME 700 COMPOUNDS WERE SYNTHESIZED AND TESTED BEFORE THE DISCOVERY OF A HISTAMINE ANTAGONIST--BURIMAMIDE--WAS FOUND THAT COMPETES WITH HISTAMINE AT THE H_2 SITE THUS BLOCKING THE SECRETION OF GASTRIC ACID. THIS IDENTIFICATION OF A COMPETITIVE ANTAGONIST CONFIRMED THE EXISTENCE OF THE H^2 RECEPTOR. THUS, THE MAJOR STEP HAD BEEN TAKEN THAT LED EVENTUALLY TO THE SYNTHESIS OF CIMETIDINE, WHICH AFTER EXTENSIVE CLINICAL TRIALS WAS AVAILABLE FOR CLINICAL USE BY 1980.

IT IS GENERALLY ACKNOWLEDGED THAT A CONTINUING NEED EXISTS TO DEVELOP PHARMACEUTICAL AGENTS THAT HAVE AS THEIR TARGET A SPECIFIC MACROMOLECULE, OR EVEN A SPECIFIC REGION OF THAT MACROMOLECULE.

- RECENT ADVANCES HAVE, IN FACT, PROVIDED AN UNPRECEDENTED OPPORTUNITY FOR THE DEVELOPMENT OF A RATIONALE TO GUIDE THE DESIGN OF DRUGS THAT INTERACT WITH SUCH TARGET MACROMOLECULES.

- FOR INSTANCE, WHEREVER A SPECIFIC NUCLEIC ACID SEQUENCE CAN BE IDENTIFIED THAT IS ESSENTIAL TO THE REPLICATION OF A VIRUS, IT MAY BE POSSIBLE TO DEVELOP A DRUG THAT CAN BIND SPECIFICALLY TO THAT REGION, OR TO ITS MESSENGER RNA THUS INHIBITING ITS FUNCTIONING

RECENTLY MICHAEL ROSSMANN AT PURDUE WITH NIAID AND NCI SUPPORT HAVE DETERMINED THE COMPLETE, THREE-DIMENSIONAL ARCHITECTURE OF A COMMON COLD VIRUS, THE RHINOVIRUS, FROM X-RAY CRYSTALLOGRAPHY STUDIES USING A HIGH ENERGY SYNCHROTRON SOURCE AND A SUPERCOMPUTER. SCIENTISTS HAVE LONG KNOWN THE GENERAL SHAPE OF THE COLD VIRUS, WHICH UNDER THE ELECTRON MICROSCOPE SHOWS AN OUTER WALL COMPOSED OF 20 TRIANGLES THAT FIT TOGETHER TO FORM THE GEOMETRIC SHAPE KNOWN AS AN ICOSAHEDRON. INSIDE THE HOLLOW PROTEIN SHELL IS THE GENETIC MATERIAL WHICH, WHEN RELEASED, DIRECTS THE CELL TO REPLICATE THE VIRUS.

THE NEW STUDIES PROVIDE A STEREO VIEW OF THE EXACT POSITION OF THE MOLECULES MAKING UP THE PROTEIN STRUCTURE SHOWING THAT EACH TRIANGLE OF THE PROTEIN SHELL HAS PEAKS AND VALLEYS FORMED BY THE IRREGULAR SHAPE OF THE PROTEIN MOLECULES MAKING UP THE SHELL. THE PART OF THE SHELL THAT MUST ATTACH TO A CELL TO CAUSE INFECTION LIES WITHIN A DEEP CLEFT OR CANYON ON EACH OF THE TRIANGULAR SIDES AND APPEARS TO BE TOO NARROW FOR ANTIBODIES TO REACH. HOWEVER, THIS FINDING RAISES THE POSSIBILITY THAT A MOLECULE COULD BE SYNTHESIZED THAT WOULD BE SMALL ENOUGH TO ENTER THE CANYON AND BIND TO THE ATTACHMENT SITE, PREVENTING ATTACHMENT OF THE VIRUS TO THE CELL AND CONSEQUENTLY PREVENTING INFECTION.

TECHNOLOGICAL ADVANCES IN SUCH AREAS AS MAGNETIC RESONANCE IMAGING PROVIDE NEW OPPORTUNITIES TO INVESTIGATE THE STRUCTURAL PROPERTIES OF PHYSIOLOGICALLY ACTIVE MOLEULES. ONE OF THE MOST REVEALING AND RAPIDLY EVOLVING RESEARCH TOOLS NOW BEING USED BY MOLECULAR BIOLOGISTS IS MAGNETIC RESONANCE IMAGING SPECTROSCOPY. WITH THIS TECHNIQUE IT IS POSSIBLE TO DETERMINE THE CHEMICAL COMPOSITION OF BIOLOGICALLY IMPORTANT MOLECULES, THE LENGTH AND NATURE OF THE BONDS HOLDING THE ATOMS OF THE MOLECULES TOGETHER, AND THE THREE-DIMENSIONAL ARRANGEMENT OF THESE MOLECULES. A SIGNIFICANT ADVANTAGE OF THIS TECHNIQUE IS THAT STUDIES CAN NOW BE PERFORMED ON MOLECULES IN THEIR TYPICAL PHYSIOLOGICALLY ACTIVE STATE, THAT IS, EITHER WITHIN THE LIVING ORGANISM OR IN AQUEOUS SOLUTION RATHER THAN IN AN UNNATURAL SOLID STATE.

THESE ADVANCES ARE REMINDERS OF WHAT NOBELIST CHRISTIAN DE DUVE HAS DESCRIBED AS "THE CRUCIAL ROLE OF INSTRUMENTS AND TECHIQUES IN THE PROGRESS OF SCIENCE. NOT THAT THE CREATIVE FACULTIES OF INTELLECT, INTUITION, IMAGINATION, SOMETIMES EVEN GENIUS MAY NOT BE OF CRITICAL SIGNIFICANCE AT SOME

STAGE. BUT," DE DUVE WENT ON TO SAY, "THESE FACULTIES ARE POWERLESS WITHOUT THE MEANS OF ESTABLISHING CONTACT WITH REALITY." HE QUOTED HIS COLLEAGUE ALBERT CLAUDE WHO HAD OBSERVED THAT "IN THE HISTORY OF CYTOLOGY, IT IS REPEATEDLY FOUND THAT FURTHER ADVANCE HAD TO AWAIT THE ACCIDENT OF TECHNICAL PROGRESS."[1]

IN STUDIES OF STRUCTURAL BIOLOGY WE ALSO SEE MANY EXAMPLES OF HOW NEW KNOWLEDGE GAINED IN ONE FIELD CAN BE APPLIED SUCCESSFULLY TO THE SOLUTION OF PROBLEMS IN ENTIRELY DIFFERENT FIELDS OF STUDY. AS SCIENCE HAS GROWN MORE SOPHISTICATED AND FOCUSES ON PROBLEMS OF INCREASING COMPLEXITY, COLLABORATION HAS GROWN BETWEEN SCIENTISTS FROM VARIOUS DISCIPLINES. THIS MOVEMENT TOWARD MULTIDISCIPLINARY RESEARCH HAS FOSTERED COMMUNICATION BETWEEN SCIENTIFIC DISCIPLINES AND HAS PROVIDED APPROACHES TO RESEARCH PROBLEMS THAT EARLIER HAD REMAINED INTRACTABLE.

IN A DIFFERENT TIME, AND PERHAPS ON A DIFFERENT SCALE, THE ESTABLISHMENT OF FASEB WAS ITSELF A MOVEMENT TOWARD A COALESCENCE OF DISCIPLINES. IN THE LATTER PART OF THE NINETEENTH CENTURY AND AT THE BEGINNING OF THE TWENTIETH A BLOSSOMING OF THE BIOLOGICAL SCIENCES TOOK PLACE, AND AS INSIGHTS DEEPENED IN PHYSIOLOGY, BIOCHEMISTRY AND PHARMACOLOGY INDEPENDENT SOCIETIES WERE FORMED TO NURTURE, THROUGH COMMUNICATION AND ASSOCIATION, THE ADVANCES BEING MADE IN THESE FOUNDATION AREAS. BUT IN 1912 IT WAS ALSO UNDERSTOOD THAT THERE WERE MANY COMMON THREADS RUNNING THROUGH THESE DISCIPLINES AND THAT ALL COULD BE STRENGTHENED THROUGH FEDERATION, AND THUS FASEB CAME INTO BEING.

NOBELIST ARTHUR KORNBERG IN COMMENTING ON THE JOINING OF MANY DISCIPLINES MADE A POINT WORTH REPEATING. HE NOTED THAT "ALTHOUGH MUCH HAS BEEN SAID AND WRITTEN OF THE EXTRAORDINARY DEVELOPMENTS IN GENETIC CHEMISTRY AND IMMUNOLOGY, THERE IS AN EVEN MORE PROFOUND DEVELOPMENT IN MEDICAL SCIENCE, A CHANGE THAT IS TRULY REVOLUTIONARY.... IT IS THE CONFLUENCE OF THE MANY DISCRETE AND PREVIOUSLY UNRELATED MEDICAL SCIENCE SUBJECTS INTO A SINGLE UNIFIED DISCIPLINE; ANATOMY, PHYSIOLOGY, BIOCHEMISTRY, MICROBIOLOGY, IMMUNOLOGY AND GENETICS HAVE NOW MERGED AND ARE EXPRESSED IN COMMON LANGUAGE OF CHEMISTRY."

WITHIN NIH WE HAVE CONCLUDED THAT A SPECIAL INITIATIVE IS NEEDED TO PROVIDE A SOUND, SCIENTIFIC, MULTIDISCIPLINARY APPROACH TO THE DEVELOPMENT OF TARGETED ANTIVIRAL COMPOUNDS THAT MAY INHIBIT ONE OR MORE CRITICAL FUNCTIONS OF THE AIDS VIRUS.

IN RESPONSE TO THIS NEED WE HAVE DEVELOPED AN NIH PROGRAM DESIGNED TO STIMULATE BASIC RESEARCH AND MOBILIZE THE SCIENTIFIC RESOURCES AND CAPABILITIES THAT EXIST IN BOTH THE INTRAMURAL LABORATORIES AND THE UNIVERSITY AND INDUSTRIAL LABORATORIES ACROSS THE COUNTRY. TO IMPLEMENT THIS INITIATIVE, $10 MILLION WAS APPROPRIATED IN THE FY 1987 BUDGET AND A SIMILAR AMOUNT IS REQUESTED IN THE FY 1988 BUDGET TO CONTINUE THE PROGRAM.

THE PROGRAM WILL HAVE TWO COMPONENTS:

- THE INTRAMURAL COMPONENT IS INTENDED TO MOBILIZE AND DEPLOY THE VAST ARRAY OF RELEVANT SCIENTIFIC TALENT THAT IS FOUND IN THE VARIOUS LABORATORIES OF THE NIH TO BETTER FOCUS ON THE BIOLOGY AND FINE STRUCTURE OF THE AIDS VIRUS AND THE DEVELOPMENT OF SPECIFIC DRUGS THAT INHIBIT VIRAL ATTACHMENT, PENETRATION, REPLICATION, INTEGRATION, AND EXPRESSION.

- AN EXTRAMURAL COUNTERPART WILL BE ESTABLISHED THROUGH THE SUPPORT OF SEVERAL MULTIDISCIPLINARY RESEARCH GROUPS THAT WILL BE CENTERED AROUND THE SAME THEME. THESE RESEARCH GROUPS WILL ALSO PROVIDE TRAINING FOR GRADUATE STUDENTS AND POSTDOCTORAL SCIENTISTS.

- INFORMAL INTERACTIONS AND EXCHANGES OF INFORMATION AMONG ALL GROUPS IN THE PROGRAM ARE EXPECTED, AND AN ANNUAL CONFERENCE OF INTRAMURAL AND EXTRAMURAL PARTICIPANTS IS PLANNED.

IT IS ALSO CLEAR THAT THE DESIRE AND, IN FACT, THE NECESSITY TO APPROACH COMPLEX RESEARCH PROBLEMS FROM A VARIETY OF PERSPECTIVES HAS LED TO ARRANGEMENTS WHICH EXTEND BEYOND MULTIDISCIPLINARY RESEARCH, AND HAVE RESULTED IN THE MERGER OF TRADITIONAL DISCIPLINES INTO NEW "HYBRID" DISCIPLINES WHOSE NAMES BETTER REFLECT THE TRUE INTERESTS AND ACTIVITIES OF THEIR PRACTITIONERS. WE HAVE SEEN, FOR EXAMPLE, THE PROLIFERATION OF SUCH INTEREST AREAS AS IMMUNOPHARMACOLOGY, NEUROBIOLOGY, STRUCTURAL BIOLOGY,

PHARMACOGENETICS, AND MANY OTHERS.

THIS MERGER OF TRADITIONAL DISCIPLINES GOES BEYOND MERELY THE ASSEMBLY OF NEW NAMES. THE BLENDING OF DISCIPLINES INTO NOVEL RESEARCH APPROACHES HAS HAD DRAMATIC RESULTS IN TERMS OF RESEARCH ACCOMPLISHMENTS.

MOLECULAR BIOLOGY HAS PROGRESSED TO THE POINT WHERE IT IS NOW POSSIBLE TO CHARACTERIZE THE HUMAN GENOME BY OBTAINING COMPLETE NUCLEOTIDE SEQUENCES OF ITS THREE BILLION COMPONENTS. THIS NEW KNOWLEDGE WOULD GREATLY ENHANCE OUR UNDERSTANDING OF THE MOLECULAR MECHANISMS THAT CONTROL GENE EXPRESSION AND THE MOLECULAR BASES FOR INHERITED DISEASE; WE WOULD GAIN SUBSTANTIAL NEW INFORMATION ON NEOPLASTIC AND MALIGNANT DISORDERS AS WELL AS ON AUTOIMMUNE AND IMMUNE DEFICIENCY DISEASES. THE INFORMATION TO BE GAINED FROM CHARACTERIZING THE HUMAN GENOME WOULD CREATE AN EXTENSIVE NEW SCIENCE BASE OF SPECIAL IMPORTANCE TO STUDIES OF TOXICOLOGY AND THE EFFECTS OF ENVIRONMENTAL CONTAMINANTS, AND THE POTENTIAL FOR EFFECTIVE GENE THERAPY WOULD BE ENHANCED. THE MOST PRESSING PROBLEM INVOLVED IN THE GENOME PROJECT IS TO DEVISE A MEANS FOR DEALING WITH THE VAST AMOUNT OF DATA THAT WILL BE GENERATED IN THE COURSE OF IT. DATABASES ESTABLISHED TO HANDLE DNA SEQUENCE INFORMATION ARE CURRENTLY SWAMPED. THE UNITED STATES' DATABASE, GENBANK, WAS PLANNED AND LAUNCHED BY THE NIH'S NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES. IT IS FUNDED AS AN INTERAGENCY PROJECT, INVOLVING THE DEPARTMENTS OF ENERGY AND DEFENSE, AND THE NATIONAL SCIENCE FOUNDATION, AS WELL AS FOUR COMPONENTS OF THE NIH. GENBANK IS LOCATED AT THE LOS ALAMOS NATIONAL LABORATORY. FORMAL ARRANGEMENTS WERE ESTABLISHED IN 1982 BETWEEN GENBANK AND THE EUROPEAN MOLECULAR BIOLOGY LABORATORY AT HEIDELBERG. IT HAS BEEN ESTIMATED THAT BOTH OF THESE BASES HAVE GROWN 25 FOLD IN THE SHORT TIME THEY HAVE BEEN IN OPERATION, AND THAT THE GENOME PROJECT WOULD CALL FOR THE HANDLING AND STORAGE OF 1000 TIMES AS MUCH INFORMATION AS IS CURRENTLY BEING PROCESSED.

SENTIMENT IN THE SCIENTIFIC COMMUNITY AT THIS TIME FAVORS APPROACHING THIS MASSIVE PROJECT THROUGH A CAREFULLY PLANNED, STEPWISE EFFORT RATHER THAN A MASS ATTACK. IN PREPARATION FOR FURTHER EFFORTS ON THE PROJECT, WE ARE DEVELOPING COLLABORATIVE ARRANGEMENTS WITH THE SCIENTIFIC COMMUNITIES IN EUROPE AND JAPAN, AND COOPERATING WITH OTHER FEDERAL AGENCIES HAVING INTEREST.

IN REVIEWING THE HISTORICAL SKETCH OF THE SOCIETY THAT APPEARED IN THE RECENT FEDERATION PROCEEDINGS, I WAS INTERESTED TO NOTE THAT AT THE TIME ASPET WAS ORGANIZED NO MEMBERS OF THE PHARMACEUTICAL INDUSTRY WERE INCLUDED AND THAT IT WAS MANY YEARS BEFORE THEY WERE ALLOWED MEMBERSHIP IN THE SOCIETY.

THIS CIRCUMSTANCE BRINGS TO MIND THE GROWING COLLABORATION AMONG INDUSTRY, GOVERNMENT AND ACADEMIA IN BIOMEDICAL RESEARCH. IN RECENT YEARS WE HAVE SEEN INCREASING SUPPORT BY INDUSTRY OF RESEARCH CONDUCTED AT ACADEMIC INSTITUTIONS. THIS DEVELOPMENT HAS INTRODUCED A THIRD PARTY INTO THE EXISTING PARTNERSHIP BETWEEN ACADEMIC INSTITUTIONS AND THE GOVERNMENT, PARTICULARLY THE NIH. THE NIH HAS A SUBSTANTIAL INTEREST IN THE OUTCOME OF THESE NEW RELATIONSHIPS AND THERE HAVE BEEN SUGGESTIONS THAT WE BECOME INVOLVED IN SOME OFFICIAL WAY WITH THEM. WE HAVE NOT DONE SO BECAUSE WE BELIEVE THESE NEW FORMS OF JOINT ENDEAVOR SHOULD CONTINUE TO EVOLVE.

INDUSTRY IS PERFORMING AND SUPPORTING AN INCREASING AMOUNT OF BIOMEDICAL RESEARCH. TWENTY YEARS AGO INDUSTRY WAS THE SOURCE OF FUNDING FOR 24 PERCENT OF HEALTH-RELATED RESEARCH AND DEVELOPMENT. IN 1986 IT FUNDED OR CONDUCTED 39 PERCENT. SUCH SUPPORT BY INDUSTRY FIRST SURPASSED NIH IN 1983. IN 1986 NIH'S SHARE WAS 35 PERCENT.

IT IS CLEARLY PREDICTABLE, HOWEVER, THAT THE FEDERAL GOVERNMENT WILL CONTINUE TO BE THE PRINCIPAL SOURCE OF FUNDING FOR BASIC RESEARCH.

AS WE CONTEMPLATE THE YEARS AHEAD--FROM THE PERSPECTIVE OF THE BEGINNING OF NIH'S SECOND CENTURY OF SCIENCE FOR HEALTH--IT IS INSTRUCTIVE TO GIVE THOUGHT TO TWO QUITE DIFFERENT EVALUATIONS OF THE PRESENT, BOTH OF WHICH ARE SUGGESTIVE OF A PRODUCTIVE FUTURE. THE FIRST FROM NOBELIST CHRISTIAN DE DUVE, WHO ADMITTED THE DIFFICULTY OF JUDGING ONE'S OWN TIME, WENT ON TO SAY, "...ONE CANNOT HELP THE FEELING THAT THE SECOND HALF OF THIS CENTURY WILL BE REMEMBERED FOR ONE OF THE GREAT BREAKTHROUGHS OF HUMAN KNOWLEDGE--PERHAPS THE GREATEST TO DATE, AS IT CONCERNS THE BASIC MECHANISMS OF LIFE."[2]

THE OTHER QUOTATION IS IN A MUCH MORE SOMBER KEY BUT SUGGESTS THE FUNDAMENTAL CHALLENGE OF THE NEXT CENTURY. IT IS A COMMENT BY DR. LEWIS THOMAS IN HIS BOOK ON "THE MEDUSA AND SNAIL." HE OBSERVED: "IN NO OTHER CENTURY IN OUR BRIEF EXISTENCE HAVE HUMAN BEINGS LEARNED SO DEEPLY, AND SO PAINFULLY, THE EXTENT AND DEPTH OF THEIR IGNORANCE ABOUT NATURE."[3]

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2. Idem

3. LEWIS THOMAS, "THE MEDUSA AND THE SNAIL," THE VIKING PRESS, NEW YORK, 1979, P.16.

FOR RELEASE UPON DELIVERY

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.
DIRECTOR
NATIONAL INSTITUTES OF HEALTH

ON

ESTABLISHMENT OF A NATIONAL BONE MARROW TRANSPLANTATION REGISTRY

BEFORE THE

SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT
COMMITTEE ON ENERGY AND COMMERCE
U.S. HOUSE OF REPRESENTATIVES

APRIL 2, 1987

Mr. Chairman, members of the Subcommittee, I am Dr. James B. Wyngaarden, Director of the National Institutes of Health. I am accompanied by Dr. Bruce Cheson, Head of the Medical Section, Clinical Investigations Branch, National Cancer Institute. I am pleased to be here to discuss the NIH's role in implementing P.L. 98-507, the National Organ Transplantation Act and, in particular, Section 401(a) which is concerned with a national registry of volunteer non-related bone marrow donors.

As you know, the bone marrow produces the normal blood elements: red cells, white cells, and platelets. If the bone marrow ceases to function, as in aplastic anemia, or is replaced by abnormal cells, as in leukemia, then a bone marrow transplant from another individual may be useful. In order to proceed with a bone marrow transplantation, there must be assurances developed through tissue typing techniques, that marrow of a patient and a donor are adequately matched. The most likely source of suitably matched bone marrow is a sibling of the patient and indeed the predominant experience in marrow transplantation has been with sibling donors. However, since only one-third of patients for whom a transplant may be indicated will have an adequately matched sibling, alternative donor sources must be secured.

NIH Conference

In order to help assess the most appropriate ways to identify the individuals who could donate marrow to unrelated patients,

CONGRESS INCLUDED A PROVISION WITHIN THE NATIONAL ORGAN TRANSPLANTATION ACT THAT "THE SECRETARY OF HEALTH AND HUMAN SERVICES SHALL HOLD A CONFERENCE ON THE FEASIBILITY OF ESTABLISHING AND THE EFFECTIVENESS OF A NATIONAL REGISTRY OF VOLUNTEER BONE MARROW DONORS." THE CONFERENCE WAS HELD IN MAY 1985, SPONSORED BY THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID); THE NATIONAL CANCER INSTITUTE (NCI); THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI), AND THE OFFICE OF MEDICAL APPLICATIONS OF RESEARCH (OMAR) OF THE NATIONAL INSTITUTES OF HEALTH. AT THAT CONFERENCE, A BROADLY BASED PANEL, COMPOSED OF BIOMEDICAL RESEARCHERS, CLINICAL PRACTITIONERS, METHODOLOGISTS, AN ETHICIST, AND A CONSUMER ADVOCATE, CONSIDERED INFORMATION RELATIVE TO THE ESTABLISHMENT OF A NATIONAL REGISTRY. MR. CHAIRMAN, I HAVE BROUGHT A COPY OF THE TECHNOLOGY ASSESSMENT MEETING STATEMENT FOR THE RECORD. BASED ON PRESENTATIONS AND PUBLIC COMMENT, THE PANEL CONCLUDED THAT IT WAS NOT APPROPRIATE TO ESTABLISH A NATIONAL REGISTRY FOR UNRELATED BONE MARROW DONORS. THE PANEL'S CONCLUSION WAS BASED ON THE DEVELOPMENTAL NATURE OF UNRELATED BONE MARROW TRANSPLANTATION AND THE MODEST SUCCESSES ACHIEVED. AT LEAST 70 PERCENT OF PATIENTS WHO RECEIVE MARROW TRANSPLANTS DIE WITHIN A FEW MONTHS OF EITHER THE DISEASE OR THE PROCEDURE ITSELF.

THE PANEL ALSO CONSIDERED THE FOLLOWING:

- PATIENTS' NEEDS FOR INFORMATION ABOUT, AND READY ACCESS TO, BONE MARROW TRANSPLANTATION;

- THE EXISTENCE OF LOCAL DONOR REGISTRIES THROUGHOUT THE UNITED STATES THAT HAVE A PROVEN CAPABILITY AND HAVE ALSO CONSIDERED MOST CAREFULLY THE RIGHTS OF DONORS REGARDING INFORMED CONSENT, CONFIDENTIALITY, AND THE PRESERVATION OF THOSE RIGHTS; AND

- THE NEED FOR FURTHER INFORMATION REGARDING THE USEFULNESS OF BONE MARROW TRANSPLANTATION USING UNRELATED, MATCHED DONORS.

TO THIS END, THE PANEL DID URGE THE ESTABLISHMENT OF A COORDINATING CENTER, WHICH COULD FUNCTION AS A CLEARINGHOUSE, TO FACILITATE AND SPEED ACCESS OF PATIENTS TO POTENTIAL UNRELATED DONORS IN LOCAL REGISTRIES.

NAVY REGISTRY

THE DEPARTMENT OF THE NAVY'S INVOLVEMENT IN THE ESTABLISHMENT OF A NATIONAL BONE MARROW REGISTRY WAS PROMPTED BY A SEPTEMBER 1984 SENATE APPROPRIATIONS SUBCOMMITTEE REPORT (#98-536) THAT RECOMMENDED THE NAVY ALLOCATE FUNDS FROM ITS FY 1985 APPROPRIATION FOR THE PURPOSE OF ESTABLISHING SUCH A REGISTRY WITHIN ITS MEDICAL RESEARCH AND DEVELOPMENT COMMAND. THE NAVY AWARDED A CONTRACT SUPPORTING THIS PROJECT IN THE SPRING OF 1986. IT IS MY UNDERSTANDING THAT THE COST TO THE NAVY FOR FY 1986 WAS APPROXIMATELY $500,000 AND THAT ESTIMATES FOR FY 1987 ARE $1,200,000. NAVY REPRESENTATIVES HAD PARTICIPATED IN THE

PLANNING FOR THE TECHNOLOGY ASSESSMENT CONFERENCE THAT NIH HELD IN 1985 AND WERE AWARE OF THE PANEL'S FINDINGS.

IN SEPTEMBER 1986, MELVYN R. PAISLEY, ASSISTANT SECRETARY OF THE NAVY FOR RESEARCH, ENGINEERING, AND SYSTEMS, WROTE SECRETARY BOWEN REGARDING THE NAVY'S PROGRAM. ASSISTANT SECRETARY PAISLEY STATED THAT THE NAVY HAD ESTABLISHED A NATIONAL REGISTRY BY CONTRACT, BUT THAT IT DID NOT WISH TO FUND THE CONTRACT AFTER FISCAL 1987. THE LETTER INVITED THE DHHS TO MEET WITH THE NAVY TO DISCUSS THE FUTURE OF THE REGISTRY. THAT MEETING WAS HELD IN JANUARY 1987. ATTENDEES INCLUDED REPRESENTATIVES FROM THE NAVY, THE CONTRACTOR AND THE DHHS.

FOLLOWING THAT MEETING, RELEVANT NIH INSTITUTES ESTABLISHED THAT THEY DID NOT BELIEVE SUPPORTING A NATIONAL REGISTRY WAS SCIENTIFICALLY JUSTIFIABLE. IT WAS THEIR CONSENSUS THAT BONE MARROW TRANSPLANTATION, WHEN THE MARROW IS HARVESTED FROM UNRELATED DONORS, IS AN EXPERIMENTAL PROCEDURE STILL IN AN EARLY STAGE OF DEVELOPMENT AND THAT MUCH REMAINS TO BE INVESTIGATED BEFORE THIS TECHNOLOGY CAN BE CONSIDERED READY FOR WIDESPREAD USE. MY CONCURRENCE WITH THIS VIEW WAS TRANSMITTED TO ASSISTANT SECRETARY WINDOM ON MARCH 17, 1987.

CONCLUSION

IN SUMMARY, WE BELIEVE THAT THE CONCLUSIONS OF THE TECHNOLOGY ASSESSMENT MEETING HELD IN 1985 ARE STILL VALID. UNRELATED BONE

MARROW TRANSPLANTATION IS A DEVELOPING FIELD IN WHICH THERE HAS BEEN ONLY A MODEST DEGREE OF SUCCESS. IT IS NOT A PROCEDURE THAT IS EITHER RECOMMENDED OR USED ON A BROAD SCALE. THE LIMITED SUCCESS DOES WARRANT CONTINUED RESEARCH IN THE AREA, AS WELL AS ENCOURAGEMENT OF LOCAL EFFORTS TO ESTABLISH AND MAINTAIN DONOR REGISTRIES.

THANK YOU, MR. CHAIRMAN. THIS CONCLUDES MY TESTIMONY. I WOULD BE PLEASED TO ANSWER QUESTIONS.

THE NIH CENTENNIAL--LOOKING FORWARD TO THE NEXT CENTURY*

by

James B. Wyngaarden, M.D.**

- Personally, and on behalf of all of my colleagues at the National Institutes of Health, I wish to express deep appreciation to the officers and members of the American College of Physicians for arranging this symposium in observance of the NIH centennial. I am particularly grateful for the opportunity you have given me to tell a bit of the history of the growth of biomedical research during the past century, and to address briefly some of today's opportunities as well as the challenges of tomorrow.

- Giving a number of talks on the centennial and participating in various ceremonies observing the hundredth anniversary have caused me to focus attention on the 1880s. I have been struck by the intellectual ferment of the time. Biology, chemistry, and physics were in a period of discovery. It was an era in which a knowledge explosion was taking place at a rate much like the spectacular advances of the present time. It has also been interesting to me to note how many scientific institutions are observing their 100th anniversary in this decade. Just last week I spoke at the centennial celebration of the American Physiological Society. This summer the NIH and the Pasteur Institute will hold a joint seminar in observance of the 100th birthday of both institutions.

- The NIH came into being at a time when medical science in the United States lagged far behind the state of knowledge in Europe. Studies in the new discipline, bacteriology, led by Robert Koch and Louis Pasteur, were becoming widespread in Europe but few Americans had participated in those advances.

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- Shortly after establishing the one-room Laboratory of Hygiene in 1887 in the Marine Hospital Service facility on Staten Island, the Laboratory's director, Dr. Joseph J. Kinyoun, arranged to have himself assigned for six months of study in the Koch and Pasteur laboratories. His concern that the new Laboratory be soundly grounded in the most advanced biology enhanced the effectiveness of his commitment to the solution of the severe public health problems of the day. This mutually beneficial [illegible]ing of undifferentiated fundamental research with disease-oriented and clinical studies has persisted and continues to be a source of great strength to the NIH at its century mark.

- In reviewing the history of the NIH from the 1987 perspective, one could apply a variety of analyses. One approach would be to identify critical events in the organization's history--developments whose outcomes shaped its future course.

- An example of such shaping events would be the decision to move the Laboratory to Washington in 1891. This change in location defined the status of the small institution as a national resource. At first the facility was placed in a building near the capitol, but in 1904 the Laboratory was moved into newly constructed buildings in the Foggy Bottom area that were designed for research activities. The new laboratories were the Institution's home for nearly 35 years. It was during this period that many successful and heroic battles against diseases, such as typhus and pellagra, were led by such giants as Drs. Howard Taylor Ricketts and Joseph Goldberger.

- A landmark in the history of the NIH was congressional enactment of the Ransdell Act of 1930. The law changed the name of the Hygienic Laboratory to the National Institute of Health, and, even more significantly, expanded its charter from concentration on infectious diseases to the broader mission of "...ascertaining the cause, prevention and cure of disease."

o Another event that signaled a major change in NIH took place at the end of World War II when the Office of Scientific Research and Development (OSRD), then going out of existence, turned over to the NIH responsibility for the completion of some 250 wartime medical research projects in progress at universities, medical schools, and pharmaceutical companies. The high-level decision to transfer the grants to NIH's administration not only confirmed the agency's role as the principal biomedical research arm of the Federal Government, it also established extramural grants as the dominant mechanism for the support of such research.

  Although the transfer of funds from the OSRD to the NIH involved less than $1 million, the event marked the beginning of the modern NIH that currently funds some 20,000 grants at an annual cost of nearly $5 billion.

o From the beginning the NIH has placed strong emphasis on the conduct and support of basic research. In the period of rapid growth of the agency, from the early 1950s to the mid-60s, and during the subsequent years the expansion of NIH programs and funding have been associated mainly with specific diseases and categories of health problems. The names of most of the constituent institutes record the concerns that prompted the creation of such entities as the National Cancer Institute, and the National Institute of Neurological and Communicative Disorders and Stroke. But within each of the Institutes is a strong program of fundamental research, usually but not necessarily related to the categorical mission of the unit.

o Although a cure for AIDS is not in sight, and the development of a vaccine is in its very earliest stages, we should remember the truly remarkable progress that has been made against this killer disease that was unknown at the beginning of this decade. In a period of less than five years, AIDS has been recognized as being caused by a virus; the virus has been identified; we have learned how the disease is transmitted; and methods have been developed for screening blood for

the virus, for deciphering its genetic code, and for identifying the sites of infection.

- The remarkable progress that has been made against AIDS thus far and the prospect for continuation rests upon a science base accumulated over a period of years in immunology, virology, chemistry, pharmacology and molecular biology.

- The NIH is beginning to use the techniques of an essentially new discipline--structural biology--in an effort to develop antiviral drugs, including, first of all, one that will target the AIDS macromolecule. This new program involves research that is possible only because of recent advances in x-ray crystallography, biophysics, molecular modeling and computer graphics. These techniques have provided fundamental insights into the structures of proteins, the principles governing molecular arrangements and basic understanding of the relation of molecular structure to function.

- There is considerable information now on the nucleotide sequence of the viral genome but more needs to be known about the envelope gene which is essential to the attachment, penetration, and uncoating of the virus.

  And thus it appears that fundamental research on structural biology is essential to the development of the new breed of pharmaceuticals, the family of antiviral drugs.

- At this time an intensive effort is under way in the realm of basic science to extract more information about another severe problem--Alzheimer's disease. Since mid-February critical findings have been announced that many believe could help lead to discovery of the cause of this disorder that affects an estimated 2.5 million older Americans, and is the fourth leading cause of death in developed countries.

- One of the announcements concerned findings from which it can be inferred that there is a gene in a relatively restricted region of

chromosome 21 which causes Alzheimer's disease in members of those families that inherit the defective gene. Knowing the approximate location of the "Alzheimer's susceptability gene" on chromosome 21 makes it feasible to attempt to isolate it and find out how it causes the disease.

- The second announcement was to the effect that NIH scientists collaborating with a French team have found that nonfamilial Alzheimer's disease patients and Down's syndrome patients have an abnormal number of copies of the gene that makes amyloid protein, a substance associated with degenerative brain changes in Alzheimer's disease. In both groups of patients studied, the abnormal gene duplication occurs on the same critical segment of chromosome 21, which has been implicated in Down's syndrome.

- These findings, as well as other recent progress in understanding specific pathologic changes caused by Alzheimer's disease, mark what is, in fact, a radical increase in knowledge about this serious disorder, that only recently has come to be regarded as other than a natural consequence of aging.

- As is the case with regard to much basic research, it frequently is not possible to predict where it will lead.

- This unpredictability brings to mind a statement made by Dr. Caleb Finch of the University of Southern California, who wrote in an editorial that appeared in SCIENCE about two years ago. "I would not be surprised," he said, "if the major new resources required for a serious attack on Alzheimer's disease do not also benefit the basic neurosciences on the same scale as funding for cancer research has done for many areas of molecular, cell and developmental biology."

- Much of the basic research today concerns molecular biology. One result of the increasing ability of scientists to study protein and nucleic acid sequences and structures has been a rapid increase in the amount of data produced. Data banks that store this information

permit scientists to compare the sequences and structures they have determined with those that have been found in other laboratories.

- Molecular biology has progressed to the point where it is now possible to characterize the human genome by obtaining complete nucleotide sequences of its three billion components. This new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and the molecular bases for inherited disease; we would gain substantial new information on neoplastic and malignant disorders, as well as on autoimmune and immune deficiency diseases. The information to be gained from characterizing the human genome would create an extensive new science base of special importance to studies of toxicology and the effects of environmental contaminants, and the potential for effective gene therapy would be enhanced.

- The most pressing problem involved in characterizing the genome is to devise a means for dealing with the vast amount of data that will be generated. The databases established to handle DNA sequence information are currently swamped. It is estimated that the human genome project would call for handling and storing 1000 times as much information as is now being processed.

- The partnership between the NIH and the health professions has produced many improvements in health care. In a substantial portion of NIH-funded research, physicians are directly involved in the scientific investigation. This collaboration usually occurs within the compass of research projects funded by NIH in hospitals and academic health centers. Such collaboration is essential in clinical research.

- The Office of Medical Applications of Research was established in January 1978 to improve the lines of communication linking the health research community to the practicing health professional and the public. The key element in this effort is "consensus development," a process that brings together biomedical research scientists, practicing physicians, consumers and others in an effort to reach general agreement on whether a given medical technology is safe and effective. This

technology may be a device, a drug, or a medical or surgical procedure. The program is aimed at complementing the usual means of reporting research results through publication.

- The National Cancer Institute's 20 Comprehensive Cancer Centers exert a significant impact on the practice of medicine. These centers are focal points for regional efforts to assure widespread use of the best available methods for early detection, diagnosis and treatment of cancer. In addition, NCI's Community Clinical Oncology Program (CCOP) links cancer specialists in private practice across the United States with cancer centers and other large cooperative groups--dispersed across the country--that conduct studies to test new cancer therapies. In a similar way the control and demonstration programs of other NIH institutes are built on a foundation of involvement of health professionals at the local level.

- Multidisciplinary General Clinical Research Centers are supported by the NIH at 78 medical centers. For more than 20 years these centers have served as foci of research, demonstration, and communication for clinical researchers across the spectrum of diseases of concern to the NIH.

- The National Library of Medicine has served physicians for a century and a half, working on a continuing basis to make biomedical information more easily accessible. Full advantage is being taken of new technologies for information storage, retrieval and transmission so that today's physician has simple and direct access to the some six-million records in NLM's computers.

- Before new preventive and therapeutic clinical regimens become routine medical practice, it is usual to validate their safety and efficacy through clinical trials and specific clinical research protocols. Currently over $400 million per year are being expended by the NIH for clinical trials. Forty-eight major new trials are scheduled for Fiscal Year 1987 at a cost of over $70 million.

- Clinical trials are among the most important and most powerful tools available to the clinical investigator. But they are expensive in terms of the effort and time they require. To avoid tragic waste in lost opportunities, as well as in dollars, it is essential that trials be critically designed and that their results be rigidly interpreted.

- If the current rate of progress in biomedical research is to be sustained, there must be an ample number of physicians having substantial training in the information, concepts, and methods of complex modern science. The trends of the past decade reflect the progressive professionalization of biomedical research--in particular clinical research.

- The importance of more and better quality training for our future physician-scientists cannot be over emphasized. Recent analyses by NIH have indicated that as far as M.D. postdoctoral trainees are concerned, the longer they have trained, the more likely they are to apply for and receive an NIH research grant. Unless they have a minimum of three years of solid research training, they usually are not successful in competing for grants. The message is clear--more research training, for most, yields a greater chance of success in gaining independent research support.

- NIH has an array of opportunities designed with M.D.s in mind:
  The six-year MSTP is considered one of our most successful in terms of building up clinical research. The program now supports about 675 students per year. Seventy percent of the graduates hold positions in academic medicine.

- NIH also has opportunities for short-term training for students in health professional schools. These programs are based on our view of the importance of early exposure to research in "capturing" clinical investigators for careers in science.

- There are a number of NIH intramural training opportunities. The NIH-HHMI program--now in its second year--brings about 30 medical

students to NIH annually. The Clinical Electives Program for medical and dental students is used by about 175 students each year who use their own finances for living expenses for an 8-10-week experience.

o We are encouraged to note that a drop off of interest of young physicians in research appears to have halted and the situation has improved somewhat in the last few years.

o As we give attention to training we are at the same time preparing for the future, even though none of us is wise enough to predict with any certainty where the growing tide of discovery will take us. The past few decades have been a time of remarkable expansion of knowledge. Nobelist Christian De Duve has remarked "....one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge--perhaps the greatest to date, as it concerns the basic mechanisms of life."[1]

In a much more somber mood, Lewis Thomas has made a statement that is complementary and implicit within it is a challenge appropriate to observance of the NIH Centennial. He observes, "In no other century in our brief existence have human beings learned so deeply, and so painfully, the extent and depth of their ignorance about nature."[2]

o In closing I will quote another reference to the NIH centennial and to the years ahead. This statement appeared in the excellent article in the current American College of Physicians Observer, titled "NIH at 100; From the Gene to the Bedside."

The comment was from my friend ACP President Emeritus Stuart Bondurant. He noted that "The NIH accomplishments have been great, but what we can most honor during this centennial is having put into place an organization, resources, and tools which can let us address the unanswered questions."

REFERENCES

[1]Christian De Duve, "A Guided Tour of the Living Cell," The Rockefeller University Press, New York, 1984, Vol 1, p. 17.

[2]Lewis Thomas, "The Medusa and the Snail," The Viking Press, New York, 1979, p. 16.

APPLICATION OF MOLECULAR BIOLOGY TO CLINICAL MEDICINE*

By
JAMES B. WYNGAARDEN**

INTRODUCTION

- Discussion of molecular biology before the program directors of the GCRCs is particularly appropriate because the practical applications of this science are daily being introduced into clinical settings. In many ways, the GCRCs provide the ideal milieux for early trials of molecular biological techniques and approaches to solving human problems.

- The growth of this field has been characterized by a dependence upon understandings from bacterial genetics, the joining of biochemistry and genetics, and the development of improved techniques for studying macromolecules.

- I am especially happy to have the opportunity to address this topic because the most significant contribution of the NIH has been the support of pioneering work in molecular biology that began to flower in the 1950s and continues unabated. This research has led to a virtual revolution extending across all the biological sciences. It is the foundation for the recombinant DNA technique whose possibilities are only beginning to be realized. An entirely new biotechnology industry is based on the recombinant DNA discoveries. Another offshoot of the long-time basic research conducted and supported by the NIH is the oncogene concept that promises a new era of understanding of cancer at the most fundamental level.

- The power of molecular biology, which focuses on the once unknown territory between the features visible to the morphologist and the small molecules of the biochemist, has worked its effect on a broad range of sciences and has altered the nature of the biological community.

- As science has grown more sophisticated in recent decades and has begun to focus on problems of increasing complexity, collaboration has grown between scientists from various disciplines. This movement toward multidisciplinary research has fostered communication between scientific disciplines and has provided approaches to research problems that earlier had remained intractable.

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*Keynote Address at General Clinical Research Center Directors Conference Williamsburg, Virginia, April 9, 1987.

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STRUCTURAL BIOLOGY

- Inasmuch as my first research was in the realm of pharmacology, the recent spectacular advances in pharmacology are especially exciting to me. In what seems a very short time, this discipline has moved into a new era, primarily due to applications of the understandings and techniques of molecular biology.

- Over the centuries, and in fact until very recently, drugs have been discovered largely in a hit-or-miss fashion. Because they have been observed to be effective in the treatment of disease, many compounds have been accepted as drugs despite an incomplete understanding of their mechanisms of action and their sometimes serious side effects. It is only in the past few years that new analytical techniques and computer programs have made it possible to design new or improved drugs with fewer side-effects, and in many instances having enhanced pharmaceutical activity.

- The story of cimetidine is an illustration of the kinds of strategies and techniques required for the development of a drug tailor-made for a specific purpose. In this instance the purpose was to make a totally new type of drug that would prevent stomach ulcers.

  It had been observed that histamine is present in large amounts in the gastric juice of ulcer patients. On the basis of successful treatment of allergic reactions with antihistamines, it was postulated that a similar approach would work in the GI tract, but the classic antihistamines (designated as H_1 blocking agents) were ineffective against gastric acid secretion.[1] From this fact it was assumed that there were two different histamine receptors on cell surfaces. Sir James Black and associates then intensified their search for an antagonist that would block histamine at a second receptor site in the acid secreting cells of the stomach, if, in fact, an H_2 receptor site existed. Some 700 compounds were synthesized and tested before the discovery of a histamine antagonist--burimamide--was found that competes with histamine at the H_2 site thus blocking the secretion of gastric acid. This identification of a competitive antagonist confirmed the existence of the H_2 receptor. Thus, the major step had been taken that led eventually to the synthesis of cimetidine, which after extensive clinical trials was available for clinical use in 1980.

    - Recent advances have, in fact, provided an unprecedent opportunity for the development of a rationale to guide the design of drugs that interact with such target macromolecules.

    - For instance, wherever a specific nucleic acid sequence can be identified that is essential to the replication of a virus, it may be possible to develop a drug that can bind specifically to that region, thus inhibiting its functioning.

- Recently Rossman and colleagues have determined the complete, three-dimensional architecture of a common cold virus (rhinovirus) from x-ray crystallography studies using a high energy synchrotron source. Scientists have long known the general shape of the cold virus, which under the electron microscope shows an outer wall composed of 20 triangles that fit together to form the geometric shape known as an icosahedron. Inside the hollow protein shell is the genetic material which, when released, directs the cell to replicate the virus.

- The new studies provide a stereo view of the exact position of the molecules making up the protein structure showing that each triangle of the protein shell has peaks and valleys formed by the irregular shape of the protein molecules making up the shell. The part of the shell that must attach to a cell to cause infection lies within a deep cleft or canyon on each of the triangular sides and appears to be too narrow for antibodies to reach. However, this finding raises the possibility that a molecule could be synthesized that would be small enough to enter the canyon and bind to the attachment site, preventing attachment of the virus to the cell and consequently preventing infection.

- Technological advances in areas such as x-ray crystallography and magnetic resonance imaging provide new opportunities to investigate the structural properties of physiologically active molecules. One of the most revealing and rapidly evolving research tools now being used by molecular biologists is magnetic resonance imaging spectroscopy. Using this technique it is possible to determine the chemical composition of biologically important molecules, the length and nature of the bonds holding the atoms of the molecules together, and the three-dimensional arrangement of these molecules. A significant advantage of this technique is that studies can now be performed on molecules in their typical physiologically active state, that is, either within the living organism or in aqueous solution rather than in an unnatural solid state.

- These advances are reminders of what Nobelist Christian de Duve has described as "the crucial role of instruments and techniques in the progress of science, not that the creative faculties of intellect, intuition, imagination, sometimes even genius may not be of critical significance at some stage, but, " de Duve went on to say, "these faculties are powerless without the means of establishing contact with reality." He quoted his colleague Albert Claude who had observed that "in the history of cytology, it is repeatedly found that further advance had to await the accident of technical progress." (Christian de Duve,"A Guided Tour of the Living Cell," the Rockefeller University Press, New York, 1984, Vol 1, p. 17).

- This kind of approach--whereby we attempt to learn more intimately about how nature designs proteins and then to improve upon nature--has come to be called protein engineering.

- o There have been some striking early results: For example, calcitonin has been redesigned by scientists at Rockefeller University. The man-made hormone, like the natural substance, regulates calcium levels in the blood, although two-thirds of its chemicaL composition is different. A redesigned calcitonin could prove better than the natural protein at treating Paget's disease and osteoporosis. With a single minor change in the structure of another protein, antitrypsin, a group of scientists in New Zealand created a molecule that could become a promising treatment for emphysema. The modified protein seems better than natural antitrypsin at inhibiting the substance causing lung tissue damage.

- o Scientists are doing interesting structural studies in rhodopsin, a protein involved in vision. These studies are giving information about the mechanism of rhodopsin's action and how the molecule's shape changes as it performs its function. Other studies have focused on bacteriorhodopsin, a protein found in the membrane of a photosynthetic bacterium that traps the energy of light and uses it to move protons across the cell membrane.

- o Related studies are also being made of beta-catecholamines, the neurotransmitters that bind to beta-adrenergic receptors on the cell surface. These receptors get their message across the membrane and into the cell by means of "signal transducers" called G proteins, which in turn stimulate the enzyme adenylate cyclase that then initiates a chain of events leading to the regulation of proteins within the cell. G proteins are also involved in the light-rhodopsin system: light activates the G protein transducin, which is then responsible for activating rhodopsin.

- o Scientists are cloning and sequencing the genes for receptors, G proteins and rhodoposin with the goal of understanding what goes on when a neurotransmitter or light stimulates a receptor to activate a G protein, and what the G protein does to activate rhodopsin or adenylate cyclase.

- o The promise of these new approaches to drug development has led NIH toward a special initiative to develop targeted antiviral compounds, particularly focused on AIDS.

- o We have developed an NIH program designed to stimulate basic research and mobilize the scientific resources and capabilities that exist in both the intramural laboratories and the university and industrial laboratories across the country. To implement this initiative, $10 million was appropriated in the FY 1987 budget and a similar amount is requested in the FY 1988 budget to continue the program.

- o The program will have two components, an intramural and an extramural component.
    - oo The intramural component is intended to mobilize and deploy the vast array of relevant scientific

talent found in the various laboratories of the NIH to better focus on the biology and fine structure of viruses and the development of specific drugs that inhibit viral attachment, penetration, replication, integration, and expression.

oo An extramural counterpart will be established through the support of several multidisciplinary research groups that will also be centered around the theme of the application of structural biology to the development of targeted antiviral drugs. These research groups will also provide training for graduate students and postdoctoral scientists.

o It is expected that these efforts will bring together multidisciplinary teams of scientists in such areas as x-ray crystallography, nuclear magnetic resonance, molecular modeling, drug design synthesis, and virology.

AIDS

o The NIH and the scientific community has been able to respond to the challenge of AIDS in a remarkable way because of an enormous investment in fundamental research over the years. When AIDS first was recognized in 1981, that prior investment in basic research had already generated a wealth of fundamental knowledge in such areas as immunoregulation, basic virology, opportunistic pathogens, the retroviruses, and DNA recombination. Without the benefit of these modern understandings and technologies, it would have been impossible even to identify and characterize AIDS, not to mention the virus causing it.

o As many of you know, the NIAID/NCI National Cooperative Drug Discovery Groups for the Treatment of AIDS that was initiated in 1986, provides a broad-based program that incorporates a variety of approaches directed toward the discovery of more effective therapies for the treatment of AIDS.

o The program is designed to include a comprehensive array of activities involving grant support for research leading to the development of new candidate anti-HTLV-III drugs, contract support for screening units to evaluate candidate drugs for in vitro anti-HTLV-III activity, preclinical testing in animals, selection of drugs for further testing, and phase I and phase II clinical testing conducted in AIDS Treatment Evaluation Units throughout the country.

o Currently 16 of the 19 AIDS Treatment and Evaluation Units (ATEUs) are funded by NIAID at institutions with GCRCs. In addition to the ATEUs,

investigators at several GCRCs have investigator-initiated support or participate in AIDS cooperative agreements for AIDS related research. Currently, at least 20 GCRCs are involved with studies defining the natural history of AIDS, the effect of treatment of infected patients with either immunomodulating agents or drugs which affect the replication of the AIDS virus. Other investigators are testing various agents and combinations of agents to treat opportunistic infections in AIDS victims. Although intervention studies are preliminary, some interesting and potentially important observations have been made.

- o NIH is encouraging efforts to exploit leads growing out of research in virology, immunology, molecular biology, protein chemistry, organic chemistry, medicinal chemistry, and pharmacology, as well as the disciplines bearing on the area of structural biology.

- o In addition, the National Institute of Allergy and Infectious Diseases (NIAID) has issued a Request for Applications (RFA) for research on "Biological and Biophysical Properties of HTLV-III/LAV and Related Retroviruses."

    - oo The NIAID's solicitation is based on the fact that while considerable information is now available on the nucleotide sequence of the viral genome, much more needs to be known about the biological, biochemical, and biophysical properties of HIV and other related retroviruses.

        - -- An improved understanding of the structural properties of the env gene, for example, is essential in order to determine the mechanisms of viral attachment, penetration, and uncoating. This information, in turn, has important implications for other research focused on the development of vaccines as well as antiviral agents.

    - oo The NIAID's RFA invites applications for regular research (R01) grants to determine the three dimensional structure of envelope glycoproteins, reverse transcriptase, gag protein, and other viral components and to relate structural studies to biological, biochemical, or biophysical processes.

GENETIC DISEASES/MAPPING THE HUMAN GENOME GENE/THERAPY

- o In years past, a number of genetic diseases--particularly inborn errors of metabolism--yielded to scientists using biochemical methods to identify the defective gene product, such as a faulty protein. They then worked back to the molecular basis of the disorder, such as

the replacement of one amino acid by another. The DNA error that produced the amino acid replacement could then be inferred.

- Now, thanks to the science of molecular genetics, it is possible to identify the gene at fault without needing to identify the primary gene product or the basic biochemical mechanism of the disease.

- The so-called "new genetics" makes it theoretically possible to diagnose any disorder that can be linked to a DNA polymorphism in a family.

- This ability was recognized first in 1978 when Kan and Dozy detected sickle cell disease by taking advantage of DNA variations that were inherited together with the presence or absence of the sickle cell gene within families.

- Researchers are now discovering so many other restriction fragment length polymorphisms (rflp's) that, in any family, a given gene defect is likely to be linked to one.

- Localization of the responsible genes have been accomplished for Huntington's disease, cystic fibrosis, Duchenne muscular dystrophy, Wilson's disease, retinoblastoma, and Alzheimer's disease.

- These gene markers are already proving useful in the clinic for genetic counseling.

- Investigators in several of the GCRCs are emerging as leaders in gene mapping and improving diagnosis of genetic diseases. For example in Tourette syndrome, multiple endocrine neoplasia syndromes, fragile X syndrome, and in defects of the urea cycle (ornithine transcarbaylase deficiency).

- To aid scientists working in related areas, the NICHD has recently funded a DNA repository to collect, catalog, and disseminate human DNA segments to be used as gene probes.

- Using such techniques as in situ hybridization and cell fusion for mapping genes whose products are known, and relying on identifiable genetic variations--such as rflp's--when necessary, plus (eventually) employing direct chromosome analysis, the possibility of mapping the entire human genome is approaching reality.

- Molecular biology has progressed to the point where it is now possible to characterize the human genome by obtaining complete nucleotide sequences of its three billion components. This new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and the molecular bases for inherited disease; we would gain substantial new information on neoplastic and malignant disorders as well as on autoimmune and immune deficiency diseases. The information to be gained from characterizing the human genome would create an extensive new science base of special importance to

studies of toxicology and the effects of environmental contaminants, and the potential for effective gene threapy would be enhanced.

- o It is clear that the technology exists for completing a major portion if not all of the task. There is general confidence that the necessary improvements in methodology will be developed to deal with certain problem areas and thus make possible the total characterization.

- o Given the available and prospective techniques, and information handling systems, what strategies are called for? All in all, while there seems to be no doubt about the wisdom of proceeding, it was the consensus at our recent Advisory Committee meeting that a carefully-planned stepwise effort rather than a mass attack is the method of choice.

- o NIH has made four decisions with regard to mapping and sequencing the human genome:

  (1) Major problems with information handling must be solved. The NIH-supported genbank--a repository for nucleic acid sequences--has already grown 25-fold in the short time it has been in operation, and the genome project would call for the handling and storage of 1000 times as much information as is currently being processed.

  (2) There is room for considerable improvement in methods for mapping and sequencing, which are occurring without special NIH incentives.

  (3) There is great interest in accelerating the mapping and sequencing of particular genes that are of clinical importance, which is being done with the usual NIH research support mechanisms.

  (4) It is early to embark on a massive program because automated instruments on the horizon hold out the prospect of reducing the ultimate cost of a mapping project by an order of magnitude or more.

- o The figure of $3 billion has been given as a cost estimate of a full program, based on a calculation that there are about 3 billion sequences in the human genome and it will cost $1 per sequence. Within a few years, however, this could be reduced to about 10 cents per sequence, dropping the total cost of the program to $300 million.

- o Human gene therapy is an area that has been moving ever closer to clinical application for the past five years or so. It is an area of high promise which seems to be stalled at present with technical problems.

- o The most likely genes to be used in the first experiments in human gene therapy are hypoxanthine-guanine phosphoribosyl transferase (HPRT), adenosine deaminase (ADA), and purine nucleoside phosphorylase

(PNP). [The disorder in each is found in the bone marrow (although for Lesch-nyhan there is absence of HPRT in brain also).]

- Earlier, it was thought that hemoglobin abnormalities might be the first targets of human gene therapy, but regulation of globin synthesis has been found to be unusually complicated.

- Clearly there are significant hurdles before human gene therapy becomes possible: For example, developing techniques to deliver corrective genes to the right cells, getting sufficient expression of those genes to make a clinical difference (many investigators have found that foreign genes are inactive when they are transferred into live animals), and verifying the safety of the procedure. In animals at least, insertion of the viral (vector) regulatory sequences in the genome may cause a cell to become cancerous if they activate. Further, difficulty remains in verifying that genes inserted into bone marrow cells are really being expressed in needed protein.

- In our enthusiasm for the promise of human gene therapy, of course, it is important to continue work on other therapeutic approaches. Just about a month ago, investigators from Duke University and the University of Nebraska reported on two children with an inherited deficiency of ADA who were treated with injections of a polyethylene glycol-modified form of the missing enzyme. The modified enzyme reportedly had a built-in extended half-life and reduced immunogenicity, mitigating two factors that have limited replacement therapy with enzymes that are normally intracellular.

- This development of modified proteins as treatment for ADA deficiency provides an exciting approach, but it is not now possible to speculate on how effective it will be in the long-term or how applicable it may be to other inherited or noninherited disorders.

- What is certain is that we need to continue to push forward the existing technologies and seek more diversity of approaches to treating genetic diseases.

- As alluded to earlier, the GCRC system can provide the ideal settings for such activity.

CANCER

- As recently as 15 years ago, it was widely believed that human retroviruses did not exist and certainly did not cause human disease. It was widely believed that no virus caused any human cancer.

- The pessimism was due to the failure to find human retroviruses after decades of searching by many investigators, and the lack of clear cut epidemiologic data. This search had been made chiefly by examining cells by electron microscopy. Thus, by 1970, further work designed to

find these viruses in humans was stopped except for a few persevering investigators.

- Robert Gallo, for one, continued to think that human retroviruses existed and caused disease, and began to develop new, sensitive and specific tests based on new molecular biological understanding of animal retroviruses.

- Between 1970 and 1975 Gallo and others working independently developed specific assays for reverse transcriptase in order to detect human retroviruses. In 1978 Gallo and co-workers isolated and characterized the first human retrovirus, called human T-cell leukemia virus (HTLV) (published in 1980). All of this early work, of course, has laid the basis for our stunning advances in understanding AIDS.

- In other areas of cancer, developments from molecular biology are moving toward clinical applications:

    - oo Understanding the activity of oncogenes is allowing scientists to look at cancer in new and more intimate ways. In the next 5-10 years these studies may yield therapeutic agents to counteract harmful oncogene products.

    - oo Already, some researchers are using oncogenes to diagnose and select therapy for patients with certain brain cancers, leukemias, and lung cancer. Others are using oncogene profiles to stage breast cancers and certain lymphomas, to distinguish tumors that are histologically similar, to determine why cancer treatment works better in some patients than others, and to see whether new treatments can be developed based on these new understandings.

- Fusion technology has yielded the ability to prepare specific monoclonal antibodies directed at many targets on tumor cells and on other cell types. Just over the past 10 years, this has created new avenues for cancer treatment. Now we can have a more rational approach, based on experimental models that define immune physiology and the dynamics of the host-tumor relationship.

- For example, scientists at the NCI (Liotta) have found that nearly all cells that are capable of metastasizing express receptors for the basement membrane protein called laminin. Tumor cells bind to laminin on the basement membrane and release collagenase that eats through the basement membrane. The tumors have also been found to express an autocrine motility factor that allows the cell to move through the opening it makes in the membrane and enter the blood stream or enter a distant cell. Obviously there are several opportunities to apply treatment strategies. In fact, efforts to block the laminin receptor

and interfere with the autocrine motility factor have been shown to reduce metastasis in animal tumor models.

- o We are just beginning to see the clinical payoffs from monoclonal antibodies in cancer research and medical practice. Three current therapeutic applications are in immune modulation, bone marrow purging and immunotherapy. In addition monocloncal antibodies have been used in diagnosis in radioimmunoassay, immunologic diagnosis of cells and tissues, and radioimmunoimaging.

HEART DISEASE AND NEUROLOGICAL DISEASE

- o One could not complete a review about applications of molecular biology to clinical medicine without mentioning the brilliant work of Michael Brown and Joseph Goldstein and others in uncovering knowledge about the genesis of atherosclerosis.

- o Most people are now familiar with their work in discovering LDL receptors in 1973.

- o This was followed by explanations of how the cell controls cholesterol metabolism through (1) regulating synthesis of HMG Co A reductase (that catalyzes a step in cholesterol's biosynthetic pathway), (2) activating the enzyme ACAT (which reattaches a fatty acid to excess cholesterol molecules, making cholesterylesters that are deposited in storage droplets), (3) driving a feedback system that stops the cell from synthesizing new LDL receptors.

- o Knowledge of the receptor deficiency in familial hypercholesterolemia (FH) suggested to Brown and Goldstein a way to help patients with the heterozygous form of the disease.

    - oo first, by interrupting the recycling of bile acids [with cholestyramine] which increases the number of LDL receptors on liver cells.

    - oo second, by using compactin (isolated from a penicillin mold) which is a natural inhibitor of HMG Co A reductase [because a piece of it binds to the enzyme's active site]. Used together, the two types of drugs were found to reduce LDL levels by about 50 percent, into the normal range.

- o Neuroscience is another area which has been blossoming since the 1970s when barriers among the disciplines of neuroanatomy, electrophysiology, neurochemistry, cell biology, and neuropharmacology began to fall and all began to borrow from molecular biology, biochemistry, immunology, and genetics.

- As Julius Axelrod has said, "The ingenious application of new technologies made it possible to ask more sophisticated and penetrating questions regarding the nervous system. Simple organisms have provided experimental models to study learning and behavior, how neurons make decisions for synaptic connections, and the isolation of receptors." (Science, September 21, 1984).

- Among the many very important advances in the neurosciences are:

    - oo discovery of many (50) neurotransmitters.

    - oo improved understanding of Huntington's disease and Alzheimer's disease because of molecular genetics and imaging technologies.

    - oo treatment of Parkinsonism and schizophrenia based on understanding neurotransmitters and receptors.

    - oo insights into plasticity of the nervous system and nerve regeneration in the C.N.S.

    - oo discoveries about the role of growth factors involved in regulating nerve and skin cells.

CONCLUSION

- These are just a few of the very exciting areas born of molecular biology which are drawing nearer to clinical applications.

- Interestingly many of these advances stemmed from the work of physician-scientists who took insights from the clinic back into the laboratory for further investigation.

- What are some conclusions that might be derived from an overview of this sort?

    - oo physicians today who wish to contribute to research need a great deal of training in the information, concepts, and methods of modern science.

    - oo they need to spend a substantial amount of time working in the laboratory, but need to interact closely with patients and with their Ph.D. colleagues. The GCRCs provide, perhaps, the perfect setting.

A SECOND CENTURY OF SCIENCE FOR HEALTH*

by

James B. Wyngaarden, M.D.**

- Our formal opening ceremony last October took place in Bethesda, and the year-long series of events in the United States and abroad will culminate in a gala celebration, including scientific symposia and an alumni reunion, in mid-October in Washington, D.C. It is a privilege for me to be here and, on behalf of the National Institutes of Health (NIH), to express our deep appreciation to all our friends and colleagues at the University of Washington for making recognition of the NIH Centennial a part of your 1987 Health Sciences Open House. Over the past several months I have had the opportunity to participate in a number of special occasions in different parts of the Nation where recognition has been given to the history of the NIH's century of science for health and to the promise of the second century.

- However, I am particularly pleased to participate in this so-called "satellite" observance. As you probably know, more than four-fifths of the current activities of the NIH take place in the academic centers, hospitals, and other non-Federal laboratories throughout the Nation. Certainly we would not feel that our 100th birthday had been observed appropriately in the absence of a very bright candle representing the University of Washington.

- There are many ties between the NIH and the University of Washington. One of the strongest bonds has been the dedicated effort on behalf of both our institutions by Warren Grant Magnuson. Both institutions bear tangible witness to his effectiveness and to the honor in which he is held--his name has been given to major facilities in both Seattle and Bethesda. You should know that the Warren Grant Magnuson Clinical Center "East" is by far the largest building on our Bethesda campus--it is the world's largest hospital devoted solely to clinical research. Many of our laboratories are located there and it is often called the "Heart of the NIH."

- All of us know that Senator Magnuson had great loyalty to the University of Washington from which he received first his undergraduate, and then his law degrees. He did not ask NIH to violate any legal or ethical restraints for the University, but he did not allow us to forget its presence.

- But the recognition he is given is for his understanding of the importance of biomedical research, an appreciation stemming partly from his experiences watching his mother suffer through serious health problems, partly from the fact that he had an active and curious mind and partly through the influence of great friends, such as Isaish Bauman at The Johns Hopkins University and Dr. Charles Mayo of Rochester, Minnesota. They encouraged his natural support for what he called "people programs."

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*Presented at the University of Washington School of Medicine in Seattle on April 10, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

As a member of the Congress he espoused the idea that "health is the first wealth of the Nation."

As a freshman Congressman in 1937 he was a sponsor of legislation to create the National Cancer Institute. In this action he was allied with another Washingtonian, Senator Homer T. Bone.

As the years went by in his distinguished career, he committed his growing influence to the support of biomedical research, and in his chairmanships of the Senate Appropriations Committee was a formidable champion of the University of Washington, of the NIH, but more importantly of the public support of biomedical research as a key to improvement of health.

- o The NIH's support of research at the University of Washington began very early in the history of our extramural programs when fellowships were awarded to E. S. Lamb for predoctoral work in zoology, and to J. M. Seigal, a chemistry major.

- o The FY 1986 NIH funding of research at the University of Washington totaled about $91 million. This included 388 grants ($78 million), 45 training grants ($6 million), 50 fellowships ($1.1 million), and 20 research contracts ($6 million).

- o In the span of years the NIH has been associated with the University of Washington both institutions have made spectacular growth.

- o Because this is a centennial event, I will take the opportunity to sketch a few chapters of NIH history and note some of our current activities.

  - NIH's beginnings were humble. We trace its origin to a one-room Marine Hospital Service laboratory on Staten Island in 1887.

  - Those modest facilities were home to the Laboratory's first Director, Dr. Joseph Kinyoun.

  - In 1891 it moved to Capitol Hill.

  - In 1904 it occupied specially constructed laboratory facilities at 25th and E Streets, N.W. This was the Institution's home for the next 35 years and site of many historial battles against disease. The first big battle to be fought there was that of Dr. Harold Taylor Ricketts, whose pioneering work on Rocky Mountain spotted fever provided the key to one of the great plagues of mankind, epidemic typhus, named for him--Rickettsia. Ricketts himself died of typhus in 1910.

  - Two years later, in 1912, Dr. T. B. McLintock went to Montana to complete a project planned by Dr. Ricketts, an investigation of spotted fever. He, too, died in the process of carrying out his investigation.

- o Another pioneer investigator was Dr. Joseph Goldberger. He was placed in charge of the Public Health Service investigation of the cause of pellagra, then prevalent throughout the poverty-ridden South but also a problem in 40 states and the District of Columbia.

- The Public Health Service was determined to make an attack on pellagra, then thought by most medical scientists to be caused by a particular organism. Dr. Goldberger argued that if a bacillus were the cause some of the doctors and nurses and other attendants working around the pellagra patients daily would get it. He pointed out that the one difference between the inmates in prisons and mental institutions, and the people who cared for them, was their diet. Many of the inmates suffered from pellagra, whereas their attendants did not.
- Dr. Goldberger's confirmatory investigation was a classic of epidemiology. A master of both observation and experimentation, Goldberger showed that the poor, monotonous diets common to many low-income people--diets high in carbohydrate and low in protein sources and fresh vegetables--induced pellagra when fed to volunteer convicts in a Mississippi penitentiary. In other public institutions where the disease occurred, investigators demonstrated that generous amounts of milk, eggs, meat, beans, and peas prevented it. Still, physicians who were treating pellagra at the time strongly believed that it was due to an infectious organism and would not accept Goldberger's evidence.
- As a final proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later Goldberger and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife, Mary. None contacted the disease, although it is not recorded what adverse symptoms may have resulted from these heroic experiments.
- He later developed a treatment using yeast in the diet and showed that the amino acid tryptophan was crucially related to the cause of the disease. Soon the B vitamin nicotinic acid, or niacin, was identified as a specific pellagra preventive.

o The Ransdell Act of 1930 was a landmark in our history. It changed the name of the Hygienic Laboratory to the National Institute of Health, expanding its emphasis from concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention and cure of disease." Among the events having a substantial impact on the future of NIH was the gift shortly thereafter of a large tract of land in Bethesda, Maryland, by Mr. and Mrs. Luke Wilson. In 1938, NIH moved from Foggy Bottom to its present campus which soon included six buildings. In 1940, President Franklin Delano Roosevelt dedicated one of the first buildings.

o Medical sciences made great strides in the post war era. Fields such as genetics, virology, molecular biology, biochemistry, immunology, and the neurosciences have attracted the brightest and most productive investigators of our era. Discoveries come so fast that it is almost impossible to keep up with these highly specialized fields. Newly developed instrumentation--from vacuum tubes to transistors, to computer chips; from x-rays to CAT scans, to PET, and MRI--has permitted amazing leaps in our fundamental understanding of human biology.

o In particular, today scientific attention in the biomedical field is focused on the structural biology of organisms at the <u>cellular</u> and <u>molecular</u> level and the mechanism by which they function and dysfunction.

- o NIH is using the techniques of a relatively new field, structural biology, in a special effort to develop antiviral drugs including, first of all, one that will target the AIDS macromolecule.
  - The NIH program is possible only because of recent advances in x-ray crystallography, biophysics, molecular modeling, and computer graphics, which have provided fundamental insights into the structure of proteins, the principles governing molecular arrangements, and basic understandings of the relation of structure to function and property.
  - Whenever a specific nucleic acid can be identified as essential to the replication of the AIDS virus, it is possible to design an antiviral drug that can interfere with its replication. It is also hoped that this program will lead to development of several principles and guidelines for designing and regulating antivirals.
  - The NIH program includes the NIAID/NCI National Cooperative Drug Discovery Group for the treatment of AIDS initiated in 1986.
  - While there is considerable information on the nucleotide sequence of the viral genome, more needs to be known about the structural properties of the env gene which is essential to the attachment, penetration, and uncoating of the virus.
  - NIAID also has invited applications for regular research grants to determine the three-dimensional structure of the envelope glycoproteins, reverse transcriptase, and other components of the AIDS virus.
  - Fundamental research in structural biology is also central to the development of a new breed of pharmaceuticals, the family of antiviral drugs.
  - NIGMS is also involved in the program. It has published an RFA announcing the avilability of funds for the extramural component of the program, "Structural Biology as applied to Targeted Drug Designed for the Treatment of AIDS." We hope that it will stimulate organization of multidisciplinary research groups that will investigate the structure of viral proteins, and also stimulate the training of graduate students and postdoctoral fellows.
- o Fundamental research is also responsible for the remarkable growth of a major new industry, biotechnology. This is due to a vast increase in our understanding of genetics.
  - It was just 12 years ago that many major figures in genetics, concerned about the potential hazards of recombinant DNA, called for a moratorium on such research because there were concerns in the scientific community, as well as in the general public, that new and dangerous organisms might result from it. The NIH was asked to develop guidelines that would permit advances in understanding in this emerging field while providing protection against possible dangers. We were able to do so. The Recombinant Advisory Committee was the basis for coordinating government-wide programs in risk assessment for all research and commercial applications under the Federal Coordinating Committee on Science, Engineering and Technology.

- o These research advances have lead to a major change in the scientific perception of what is possible and what is desirable. Today, scientists at NIH and elsewhere are debating the wisdom of proposals to attempt to characterize the entire three billion nucleotide human genome.

  - A decade ago, this project would have sounded like science fiction but the fact is, the technology exists today. Whether such an endeavor is practical, given our resources, is the question now being debated.

  - This project is possible because molecular biology has taught us much about mechanisms of gene expression and the molecular bases of inherited diseases (malignant neoplasms, immune deficiencies, autoimmune diseases).

  - The project could cost an estimated $3 billion and take ten years, but could have very positive outcomes:

    Four thousand (4,000) human diseases have genetic basis, including cystic fibrosis, Duchenne-type muscular dystrophy, Huntington's disease, and Alzheimer's disease.

    Could discover why some get diseases such as cancer, heart disease, mental illness, while others do not.

    Would provide exponential increase in knowledge of human biology.

- o As we contemplate the years ahead--NIH's second century of science for health--it is instructive to give thought to two quite different evaluations of the present, both of which are suggestive of a productive future. The first from Nobelist Christian De Duve, who admitted the difficulty of judging one's own time, went on to say, " . . . one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge--perhaps the greatest to date, as it concerns the basic mechanisms of life." The other quotation is in a much more somber key but suggests the fundamental challenge of the next century. Dr. Thomas commented, "In no other century in our brief existence have human beings learned so deeply, and so painfully, the extent and depth of their ignorance about nature."

DRAFT

NEW SCIENCE, NEW FRONTIERS*

BY

JAMES B. WYNGAARDEN, M.D.**

OVER THE PAST SEVERAL MONTHS I HAVE BEEN PRIVILEGED TO PARTICIPATE IN A NUMBER OF SPECIAL OCCASIONS AS A PART OF THE YEAR-LONG OBSERVANCE OF THE CENTENNIAL OF THE NATIONAL INSTITUTES OF HEALTH. IN MANY INSTANCES THE EVENT HAS BEEN A JOINT SALUTE TO THE NIH AND TO AN IMPORTANT HAPPENING IN THE LIFE OF THE HOST INSTITUTION. FOR EXAMPLE, I SPOKE AT A LUNCHEON JOINTLY HONORING THE 75TH BIRTHDAY OF FASEB AND THE 100TH BIRTHDAY OF NIH. ON THE SAME DAY I PARTICIPATED IN A SEMINAR AT THE AMERICAN PHYSIOLOGICAL SOCIETY CELEBRATING THE CENTENNIAL OF THAT ORGANIZATION. LATE NEXT MONTH THE NIH WILL HOST A SYMPOSIUM WITH THE PASTEUR INSTITUTE THAT IS BEING HELD IN RECOGNITION OF THE CENTENNIAL OF BOTH INSTITUTIONS.

o THIS IS ALSO A JOINT OBSERVANCE BUT IT IS THE FIRST ONE OF ITS KIND IN WHICH I HAVE HAD A PART. FOR WE ARE NOT ONLY MARKING PAST ACHIEVEMENTS OF A CENTURY OF SCIENCE, WE ARE ALSO PARTICIPATING IN AN IMPORTANT BEGINNING THROUGH THE DEDICATION OF A MAGNIFICENT FACILITY TO THE FUTURE OF SCIENCE.

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*ADDRESS PRESENTED AT DEDICATION OF NEW LABORATORY BUILDING AT THE OREGON HEALTH SCIENCES UNIVERSITY, PORTLAND, OREGON, APRIL 24, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

o I WISH TO EXTEND MY CONGRATULATIONS TO THE FACULTY AND TO ALL ASSOCIATED WITH THE OREGON HEALTH SCIENCES UNIVERSITY--TO MY FRIEND LEONARD LASTER--AND TO THE PEOPLE OF OREGON FOR THE SIGNIFICANT STEP FORWARD THAT THE VOLLUM INSTITUTE FOR ADVANCED BIOMEDICAL RESEARCH REPRESENTS. AND IN BEHALF OF ALL WHO ARE CONCERNED ABOUT THE CONTINUED PROGRESS OF SCIENCE, I TAKE THE LIBERTY OF EXPRESSING GRATITUDE TO MRS. HOWARD VOLLUM FOR THE LARGE CONTRIBUTION THAT SHE AND HER LATE HUSBAND HAVE MADE FOR THE HEALTH AND WELL-BEING OF THE CURRENT GENERATION AND FOR THE ONES TO FOLLOW.

o THE INSTITUTE WE DEDICATE IS AN EXPRESSION OF COMMITMENT BY THE UNIVERSITY TO THE SEARCH AT THE FRONTIERS OF SCIENCE--PARTICULARLY IN THE AREA OF NEUROBIOLOGY. DR. LASTER HAS TOLD ME THAT THE BREADTH OF VISION AND STANDARDS OF EXCELLENCE INSISTED UPON BY THE FIRST DIRECTOR, DR. EDWARD HERBERT, WILL BE MAINTAINED THROUGH THE OUTSTANDING GROUP OF YOUNG SCIENTISTS HE WAS ABLE TO ASSEMBLE PRIOR TO HIS DEATH LAST FEBRUARY.

o THE SURGE OF DISCOVERY THAT HAS TAKEN PLACE IN THE BIOSCIENCES IN LESS THAN A GENERATION IS WITHOUT PRECEDENT AND IS GATHERING STRENGTH. NOT LONG AGO, SCIENCE MAGAZINE PUBLISHED A COLLECTION OF RESEARCH PAPERS UNDER THE GENERAL HEADING OF "THE REVOLUTION IN BIOLOGY." THE LEAD ARTICLE, TITLED "BIOLOGICAL FRONTIERS," WAS WRITTEN BY BIOPHYSICIST FREDERICK R. BLATTNER. HE WROTE, "PHILOSOPHERS AND HISTORIANS OF SCIENCE WILL PROBABLY REGARD THE CURRENT PERIOD AS A TIME OF EXPLOSIVE ADVANCE AND REFINEMENT OF

INFORMATION RATHER THAN A TRUE REVOLUTION. IT HAS NOT BEEN NECESSARY, HOWEVER, AS WAS THE CASE WITH QUANTUM THEORY OR RELATIVITY, TO OVERTURN MAJOR PARADIGMS OF ACCEPTED THOUGHT, RATHER," HE SAID, "AN ENORMOUS INCREASE IN THE POWER OF EXPERIMENTAL TECHNIQUES IS NOW PRODUCING ANSWERS TO COMPLEX, LONG-STANDING BIOLOGICAL QUESTIONS."[1]

WHETHER TERMED AN EXPLOSION OR A REVOLUTION, IT IS AN EXCITING TIME, INDEED, AND ALL WHO HAVE A ROLE IN AN UNDERTAKING SUCH AS THIS ONE CAN FEEL FORTUNATE TO BE AN ACTIVE PARTICIPANT IN THE ADVANCES BEING MADE BEYOND THE OUTER LIMITS OF THE KNOWN.

CREATIVE ACTIVITY IN THE RESEARCH ENTERPRISE IS NOT CONFINED TO THE SCIENTIST AT THE BENCH OR BEDSIDE. THE SUPPORT OF SCIENCE REQUIRES A DIFFERENT DIMENSION OF CREATIVITY--A CREATIVE LEADERSHIP THAT IS COMMITTED TO CONSTRUCTING AND MAINTAINING AN ENVIRONMENT WHERE ALL PARTICIPANTS CAN BE CREATIVE. SUCH LEADERSHIP REQUIRES AN UNDERSTANDING OF THE NATURE OF SCIENCE AND A WILLINGNESS TO RISK ITS UNCERTAINTIES.

LEWIS THOMAS ONCE NOTED, "IT IS HARD TO PREDICT HOW SCIENCE IS GOING TO TURN OUT, AND IF IT IS REALLY GOOD SCIENCE, IT IS IMPOSSIBLE TO PREDICT. THIS IS THE NATURE OF THE ENTERPRISE."[2]

GRANTED THAT THERE ARE GREAT UNCERTAINTIES AS TO WHERE TOMORROW'S RESEARCH MAY LEAD, THERE IS ONE OUTCOME THAT CAN BE PREDICTED AS A RESULT OF THE INSTITUTE BEING DEDICATED. THE STRONG EMPHASIS

YOU HAVE PLACED ON THE NEUROSCIENCES WILL STRENGTHEN ALL OF THE UNIVERSITY'S RESEARCH AND TEACHING EFFORTS IN THIS AREA OF SPECTACULAR ADVANCES AND GREAT PROMISE. I AM TOLD THAT THIS PROCESS HAS ALREADY BEGUN.

ON THE NATIONAL SCENE THE NEED TO APPROACH COMPLEX RESEARCH PROBLEMS FROM A VARIETY OF PERSPECTIVES HAS LED TO ARRANGEMENTS THAT EXTEND BEYOND MULTIDISCIPLINARY RESEARCH, AND HAVE RESULTED IN THE MERGER OF TRADITIONAL DISCIPLINES INTO NEW "HYBRID" DISCIPLINES WHOSE NAMES BETTER REFLECT THE TRUE INTERESTS AND ACTIVITIES OF THEIR PRACTITIONERS. WE HAVE SEEN, FOR INSTANCE, THE PROLIFERATION OF SUCH INTEREST AREAS AS IMMUNOPHARMACOLOGY, NEUROBIOLOGY, STRUCTURAL BIOLOGY, PHARMACOGENETICS, AND MANY OTHERS.

THIS MERGER OF TRADITIONAL DISCIPLINES GOES BEYOND MERELY THE ASSEMBLY OF NEW NAMES. THE BLENDING OF DISCIPLINES INTO NOVEL RESEARCH APPROACHES HAS HAD DRAMATIC RESULTS IN TERMS OF RESEARCH ACCOMPLISHMENTS.

THE LINKAGE THAT YOU ARE MAKING BETWEEN MOLECULAR BIOLOGY AND STUDIES OF THE BRAIN IS CHARACTERISTIC OF THE CONVERGENCE OF DISCIPLINES IN THE BIOLOGICAL SCIENCES TODAY, AND FROM THIS SYNTHESIS MAY COME SOLUTIONS TO OLD AND INTRACTABLE HEALTH PROBLEMS.

AT THIS TIME AN INTENSIVE EFFORT IS UNDER WAY IN THE REALM OF BASIC SCIENCE TO EXTRACT MORE INFORMATION ABOUT ONE OF THE MOST DEVASTATING AND FEARED OF THE MANY DISORDERS ASSOCIATED WITH GROWING OLDER--ALZHEIMER'S DISEASE. THE URGENCY OF THE PROBLEM ARISES NOT ONLY FROM THE TRAGIC NATURE OF THE DISEASE, BUT ALSO FROM THE FACT THAT IT AFFECTS A SUBSTANTIAL PORTION OF OLDER PEOPLE. WITHIN THE PAST TWO MONTHS CRITICAL FINDINGS HAVE BEEN ANNOUNCED THAT MANY BELIEVE COULD HELP LEAD TO DISCOVERY OF THE CAUSE OF THIS DISORDER THAT AFFECTS AN ESTIMATED 2.5 MILLION OLDER AMERICANS, AND IS THE FOURTH LEADING CAUSE OF DEATH IN DEVELOPED COUNTRIES.

ONE OF THE RECENT ANNOUNCEMENTS CONCERNED FINDINGS FROM WHICH IT CAN BE INFERRED THAT THERE IS A GENE IN A RELATIVELY RESTRICTED REGION OF CHROMOSOME 21 THAT CAUSES ALZHEIMER'S DISEASE IN MEMBERS OF THOSE FAMILIES THAT INHERIT THE DEFECTIVE GENE. KNOWING THE APPROXIMATE LOCATION OF THE "ALZHEIMER'S SUSCEPTIBILITY GENE" ON CHROMOSOME 21 MAKES IT FEASIBLE TO ATTEMPT TO ISOLATE IT AND FIND OUT HOW IT CAUSES THE DISEASE.

THE SECOND ANNOUNCEMENT WAS TO THE EFFECT THAT NIH SCIENTISTS IN COLLABORATION WITH A FRENCH TEAM HAVE FOUND THAT NONFAMILIAL ALZHEIMER'S DISEASE PATIENTS AND DOWN'S SYNDROME PATIENTS HAVE AN ABNORMAL NUMBER OF COPIES OF THE GENE THAT MAKES AMYLOID PROTEIN, A SUBSTANCE ASSOCIATED WITH DEGENERATIVE BRAIN CHANGES IN ALZHEIMER'S DISEASE. IN BOTH GROUPS OF PATIENTS STUDIED, THE

ABNORMAL GENE DUPLICATION OCCURS ON THE SAME CRITICAL SEGMENT OF CHROMOSOME 21, WHICH HAD BEEN IMPLICATED IN DOWN'S SYNDROME.

THESE FINDINGS, AS WELL AS OTHER RECENT PROGRESS IN UNDERSTANDING SPECIFIC PATHOLOGIC CHANGES CAUSED BY ALZHEIMER'S DISEASE, MARK WHAT IS, IN FACT, A RADICAL INCREASE IN KNOWLEDGE ABOUT THIS SERIOUS DISORDER THAT ONLY RECENTLY HAS COME TO BE REGARDED AS OTHER THAN A NATURAL CONSEQUENCE OF AGING.

AS IS THE CASE WITH MUCH BASIC RESEARCH, IT FREQUENTLY IS NOT POSSIBLE TO PREDICT WHERE IT WILL LEAD. THIS CHARACTERISTIC IN THE CONTEXT OF RESEARCH ON ALZHEIMER'S DISEASE WAS ADDRESSED IN A STATEMENT BY DR. CALEB FINCH, OF THE UNIVERSITY OF SOUTHERN CALIFORNIA, WHO REMARKED, "I WOULD NOT BE SURPRISED," HE SAID, "IF THE MAJOR NEW RESOURCES REQUIRED FOR A SERIOUS ATTACK ON ALZHEIMER'S DISEASE DO NOT ALSO BENEFIT THE BASIC NEUROSCIENCES ON THE SAME SCALE AS FUNDING FOR CANCER RESEARCH HAS DONE FOR MANY AREAS OF MOLECULAR, CELL AND DEVELOPMENTAL BIOLOGY."

MUCH OF BASIC RESEARCH TODAY CONCERNS MOLECULAR BIOLOGY IN ITS MANY DIFFERENT APPLICATIONS.

AS AN EXAMPLE, SUCH STUDIES HAVE NOW PROGRESSED TO THE POINT WHERE IT IS POSSIBLE TO CHARACTERIZE THE HUMAN GENOME BY OBTAINING COMPLETE NUCLEOTIDE SEQUENCES OF ITS THREE BILLION COMPONENTS. THIS NEW KNOWLEDGE WOULD GREATLY ENHANCE OUR UNDERSTANDING OF THE MOLECULAR MECHANISMS THAT CONTROL GENE EXPRESSION AND THE

MOLECULAR BASIS FOR INHERITED DISEASE; AND WE WOULD GAIN SUBSTANTIAL NEW INFORMATION ON NEOPLASTIC AND MALIGNANT DISORDERS, AS WELL AS ON AUTOIMMUNE AND IMMUNE DEFICIENCY DISEASES. THE DATA TO BE GAINED FROM CHARACTERIZING THE HUMAN GENOME WOULD CREATE AN EXTENSIVE NEW SCIENCE BASE OF SPECIAL IMPORTANCE TO STUDIES OF TOXICOLOGY AND THE EFFECTS OF ENVIRONMENTAL CONTAMINANTS, AND THE POTENTIAL FOR EFFECTIVE GENE THERAPY WOULD BE ENHANCED.

THE SITUATION WITH REGARD TO CHARACTERIZING THE HUMAN GENOME IS SIMILAR TO THAT OBTAINING 12 YEARS AGO WHEN A GROUP OF AMERICA'S MOST DISTINGUISHED SCIENTISTS CALLED FOR A VOLUNTARY DEFERRAL OF RESEARCH ON RECOMBINANT DNA PENDING THE DEVELOPMENT OF GUIDELINES FOR THE SAFE CONDUCT OF SUCH EXPERIMENTATION. THEN, AS NOW, LEADERS IN SCIENCE HAVE REACTED PROMPTLY TO NEW ADVANCES IN TECHNIQUES THAT MAKE IT REASONABLE TO EXPECT THAT IT WILL BE POSSIBLE TO TAKE A MAJOR STEP FORWARD. THE CURRENT SITUATION, HOWEVER, DIFFERS MARKEDLY. THEN THERE WAS CONCERN ABOUT PROCEEDING BECAUSE OF THE POSSIBILITY OF UNKNOWN ENVIRONMENTAL HAZARDS. CHARACTERIZING THE HUMAN GENOME POSES NO SUCH RISKS BUT DOUBTS HAVE BEEN EXPRESSED ABOUT THE WISDOM OF COMMITTING THE ENORMOUS RESOURCES THAT WOULD BE REQUIRED FOR AN ALL-OUT ACCELERATED PROGRAM. IN COMPARING THE CHALLENGE OF THE NEW PROGRAM TO THE EARLY DAYS OF RECOMBINANT DNA, FORMER NIH DIRECTOR DONALD S. FREDRICKSON RECALLED THE SITUATION IN THE MID-70S AND REMARKED, "WE NOW FACE A NEW CHALLENGE, THIS TIME MORE AWESOME THAN DANGEROUS."

NIH HAS COME TO FOUR CONCLUSIONS WITH RESPECT TO MAPPING AND SEQUENCING THE HUMAN GENOME:

1) MAJOR PROBLEMS WITH INFORMATION HANDLING MUST BE SOLVED. THE NIH-SPONSORED GENBANK®--A REPOSITORY FOR NUCLEIC ACID SEQUENCES--HAS ALREADY GROWN 25-FOLD IN THE SHORT TIME THAT IS HAS BEEN IN OPERATION, AND THE GENOME PROJECT WOULD CALL FOR THE HANDLING AND STORAGE OF 1000 TIMES AS MUCH INFORMATION AS IS CURRENTLY BEING PROCESSED.

2) THERE IS ROOM FOR CONSIDERABLE IMPROVEMENT IN METHODS FOP MAPPING AND SEQUENCING, WHICH ARE OCCURRING WITHOUT SPECIAL NIH INITIATIVES.

3) THERE IS GREAT INTEREST IN ACCELERATING THE MAPPING AND SEQUENCING OF PARTICULAR GENES THAT ARE OF CLINICAL IMPORTANCE--AN ACTIVITY BEING SUPPORTED THROUGH THE USUAL NIH RESEARCH SUPPORT MECHANISMS.

4) IT IS EARLY TO EMBARK ON A MASSIVE PROGRAM BECAUSE AUTOMATED INSTRUMENTS ON THE HORIZON HOLD OUT THE PROSPECT OF REDUCING THE ULTIMATE COST OF MAPPING PROJECT BY AN ORDER OF MAGNITUDE OR MORE.

o THE FIGURE OF $3 BILLION HAS BEEN GIVEN AS A COST ESTIMATE OR A FULL PROGRAM, BASED ON A CALCULATION THAT THERE ARE ABOUT 3 BILLION SEQUENCES IN THE HUMAN GENOME AND THAT IT WILL COST ABOUT $1 PER SEQUENCE. WITHIN A FEW YEARS THIS COULD BE REDUCED

TO ABOUT 10 CENTS PER SEQUENCE, DROPPING THE TOTAL COST OF THE PROGRAM TO ABOUT $300 MILLION.

- A FURTHER COMMENT ABOUT HUMAN GENE THERAPY IS APPROPRIATE AT THIS POINT. THIS PROMISING TECHNIQUE HAS BEEN MOVING EVER CLOSER TO CLINICAL APPLICATION FOR THE PAST FIVE YEARS OR SO, BUT AT PRESENT PROGRESS SEEMS TO BE STALLED WITH TECHNICAL PROBLEMS.

- CLEARLY THERE ARE SIGNIFICANT HURDLES BEFORE HUMAN GENE THERAPY BECOMES POSSIBLE: FOR EXAMPLE, DEVELOPING TECHNIQUES TO DELIVER CORRECTIVE GENES TO THE RIGHT CELLS, GETTING SUFFICIENT EXPRESSION OF THOSE GENES TO MAKE A CLINICAL DIFFERENCE (MANY INVESTIGATORS HAVE FOUND THAT FOREIGN GENES ARE INACTIVE WHEN THEY ARE TRANSFERRED INTO LIVE ANIMALS), AND VERIFYING THE SAFETY OF THE PROCEDURE IN ANIMALS AT LEAST. INSERTION OF THE VIRAL (VECTOR) SEQUENCES IN THE GENOME MAY CAUSE A CELL TO BECOME CANCEROUS IF THEY ACTIVATE AN ONCOGENE. FURTHER, DIFFICULTY REMAINS IN VERIFYING THAT GENES INSERTED INTO BONE MARROW CELLS ARE REALLY BEING EXPRESSED IN NEEDED PROTEIN.

- IN OUR ENTHUSIASM FOR THE PROMISE OF HUMAN GENE THERAPY, WE CANNOT OVERLOOK THE ACCELERATING MOVEMENT ACROSS THE SPECTRUM OF LABORATORY AND CLINICAL RESEARCH. FOR, AS I MENTIONED EARLIER, IT IS A TIME OF CONVERGENCE IN SCIENCE.

- Neuroscience has blossomed since the 1970s when barriers among the disciplines of neuroanatomy, electrophysiology, neurochemistry, cell biology, and neuropharmacology began to fall and all began to borrow heavily from molecular biology, biochemistry, immunology and genetics.

- As Julius Axelrod has said, "The ingenious application of new technologies made it possible to ask more sophisticated and penetrating questions regarding the nervous system. Simple organisms have provided experimental models to study learning and behavior, how neurons make decisions for synaptic connections, and the isolation of receptors."

- Among recent important advances in the neurosciences are:
  - Discovery of at least 50 neurotransmitters.
  - Improved understanding of Huntington's disease and Alzheimer's disease through the use of molecular genetics and imaging technologies.
  - Treatment of parkinsonism and schizophrenia based on better understanding of neurotransmitters and receptors.
  - Insights into plasticity of the nervous system and nerve regeneration in the central nervous system.
  - Discoveries about the role of growth factors involved in regulating skin and nerve cells.

- The decision by the Oregon Health Sciences University to emphasize exploration at the neurobiology frontiers places the

VOLLUM INSTITUTE FOR ADVANCED BIOMEDICAL RESEARCH SQUARELY AT THE CENTER OF AN AREA OF GREAT EXCITEMENT AND GREAT POSSIBILITIES.

o AS WE CONTEMPLATE THE YEARS AHEAD--FROM THE PERSPECTIVE OF THE BEGINNING OF NIH'S SECOND CENTURY OF SCIENCE FOR HEALTH--IT IS INSTRUCTIVE TO GIVE THOUGHT TO TWO DIFFERING EVALUATIONS OF THE PRESENT, BOTH OF WHICH ARE SUGGESTIVE OF A PRODUCTIVE FUTURE. THE FIRST FROM NOBELIST CHRISTIAN DE DUBE, WHO ADMITTED THE DIFFICULTY OF JUDGING ONE'S OWN TIME, WENT ON TO SAY, "....ONE CANNOT HELP THE FEELING THAT THE SECOND HALF OF THIS CENTURY WILL BE REMEMBERED FOR ONE OF THE GREAT BREAKTHROUGHS OF HUMAN KNOWLEDGE--PERHAPS THE GREATEST TO DATE, AS IT CONCERNS THE BASIC MECHANISMS OF LIFE."[3] THE OTHER QUOTATION IS IN A MUCH MORE SOMBER KEY BUT SUGGESTS THE FUNDAMENTAL CHALLENGE OF THE NEXT CENTURY. IT IS A COMMENT BY DR. LEWIS THOMAS IN HIS BOOK ON "THE MEDUSA AND THE SNAIL." HE OBSERVED: "IN NO OTHER CENTURY IN OUR BRIEF EXISTENCE HAVE HUMAN BEINGS LEARNED SO DEEPLY, AND SO PAINFULLY, THE EXTENT AND DEPTH OF THEIR IGNORANCE ABOUT NATURE."[4]

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ADVANCING BIOMEDICAL RESEARCH: A PARTNERSHIP*

BY

JAMES BY WYNGAARDEN, M.D.**

- I am very happy to be here this afternoon to join in this seminar marking the Sesquicentennial of Rush-Presbyterian. As many of you know, the National Library of Medicine-- which is a component of the NIH--and NIH itself are also observing anniversaries. The NLM is 150 years old and the NIH is in its centennial year.

- All three of these entities--and a number of other scientific institutions and organizations marking their centennials this year (for example, the American Physiological Society and the Pasteur Institute)--were a part of the move toward scientific medicine that began in the second part of the 1800s. As William Osler put it in one of his famous essays, it was an era when "The spirit of science was upon the waters."

- It is especially noteworthy that your great institution was named for Benjamin Rush, the only physician who signed the Declaration of Independence. Not only was Rush one of the earliest medical schools west of the Mississippi, it was among the early medical schools to infuse science into its curriculum and to affiliate with an institution of higher education.

- NIH was launched with this same emphasis on science so it is not too surprising that both the founder of your medical school and the first director of the NIH (then called the Laboratory of Hygiene) spent time in the great laboratories of Europe before launching their respective institutions dedicated to health.

- The leadership demonstrated by Rush Medical School in these early days has been continued and is characterized by an ability to respond to challenges and opportunities. For example, Rush has demonstrated flexibility in responding promptly to the changing health care environment (e.g., emphasis on ambulatory medicine). Further, Rush seems to have adjusted to the fiscal climate of the 1980s: I note, for example, that research funding here is derived from a plurality of sources--government, state, private industry and foundations--and that Rush is cooperating with state and local governments and private industry in drawing industry and academia closer together in research and development efforts. (Chicago Technology Park Research Center).

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* Address at the Science and Medicine Sesquicentennial Symposium, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, April 29, 1987.

** Director, National Institutes of Health

o It is this new climate of the 1980s that really is the theme of the discussion this afternoon. I would like to discuss the three-way partnership in biomedical research that has emerged, and particularly NIH's role in this partnership.

THE NIH-ACADEMIA PARTNERSHIP

o As would be expected, the National Institutes of Health has undergone organizational changes during the past century, some approaching transformations. For the first half of its history the agency was, in essence, a small federal laboratory carrying out within its own confines important research projects, but its resources were such that at any given time only a limited number of studies could be conducted. It was during the adjustment period following World War II that the transformation took place. With demobilization the Office of Scientific Research and Development (OSRD) went out of business on December 31, 1945, and some 250 biomedical research projects funded by the OSRD at universities, hospitals and other research institutions were transferred to the NIH for administration. It is significant that the research projects were not cancelled, and that instead a mechanism was put in place for continuing to award such grants and contracts. Peacetime reliance on non-Federal laboratories for the conduct of federally-supported research represented a sea change in Federal science policy and has been responsible for the establishment of the modern NIH.

o By far, the largest part of NIH research takes place in nearly 1300 non-Federal laboratories, most of them within the United States, where more than $4 billion is being expended annually from the NIH budget for biomedical research and research training. Almost 90 percent of the NIH budget is devoted to such awards and the necessary administrative costs entailed.

o In addition to the grant and contract-supported extramural research, more than 2,500 government scientists participate in research at our main campus in Bethesda, at the National Institute of Environmental Health Sciences at the Research Triangle in North Carolina, and in a few small NIH installations elsewhere. These intramural scientists, their collaborating guest workers, and the laboratories where they perform their research constitute what is probably the largest resource of its kind. As large as it is, however, it is through our extramural programs that we mobilize the energies of some 50,000 American scientists who carry out research under NIH-awarded grants and contracts.

o Since the time NIH began to develop its extramural programs--we have adhered to several principles that have served us well over the years.

- Foremost is the conviction that basic knowledge should be pursued largely through the support of biomedical research conducted by scientists in academia, and that the capacity of those institutions (primarily medical schools) should be strengthened wherever possible.

- Another guiding principle has been that the primary source of research support should be the investigator-initiated research project grant, by which mechanism we believe we can tap the most creative minds attacking the most critical problems in science.

- A third important factor has been our reliance upon a peer review system of outside advisors for selection of the most meritorious proposals presented to us.

- Finally, the fourth element of these timeless principles is that it is essential to assure a continuing supply of well-trained scientists to conduct research in the future. There is a close interrelationship between productivity in research and the availability and replenishment of the supply of qualified investigators.

- Upon comparison with NIH, industry's involvement with academia in biomedical research has been modest. Of all the funds going to academia for health R&D, industry's share has been about 3% as compared with 77% from the Federal government.

INDUSTRY JOINS THE PARTNERSHIP

- In recent years, since the early 80s, all of us in the biomedical field have been acutely aware of industry's amplified interest in becoming a participant in the biomedical research partnership. Scientific advances and opportunities have been the drawing force behind this seemingly "new" interest on the part of industry.

- Scarcely a dozen years old, the "new biotechnology revolution" has burgeoned into a billion-dollar industry that can already be credited with having improved the safety of the U.S. blood supply in the presence of the AIDS threat, enormously enhanced the accuracy and timeliness of laboratory diagnoses, and supplied clotting factor of hemophiliacs and a vaccine against hepatitis. On the horizon are toxin-linked antibodies that home in on, and kill, cancer cells and further off, gene therapy to remedy hereditary defects. New analytical techniques, computer programs, new approaches in structural biology are making it possible to design new or improved drugs with fewer side effects and in many instances having enhanced pharmaceutical activity. And the promise of this new era goes beyond medical advances--it embraces aspects of agriculture, food processing, and chemical manufacturing.

- This amazing array is to a great extent the result of steadfast support for basic biomedical research by the National Institutes of

Health. For more than 30 years, NIH has funded pioneering investigations and research training in basic sciences--molecular genetics, molecular and cell biology, and immunology--to advance understanding of biological processes in health and disease. As this research began to unfold its potential, NIH extended its support to more focused research projects--manipulating genes, cloning DNA, and creating monoclonal antibodies. (The 1986 estimate for NIH support of research and research training underlying biotechnology is about $1.2 billion, and for more directly-related projects about $636 million.)

- o In addition, most of the men and women who today are participating in the biotech drama were trained by or through NIH. Furthermore, NIH has played a key role in piloting biotechnology's development by taking early responsibility for ensuring the safety of Federally-funded research involving recombinant DNA.

- o The tremendous opportunities for practical applications of knowledge gained from molecular biology became obvious at a time when universities and academic medical centers were facing financial difficulties and welcomed new kinds of arrangements with industry.

- o Industry sees that in order to stay competitive they need the additional ideas and trained scientists produced by academia with Federal support.

- o And, from the government--or NIH point of view-- we need the cooperative efforts of academia and industry in order to carry out our mandate to conduct and support biomedical research for the public good.

- o The economic aspect of biomedical research is neither trivial nor a misuse of science. It is an important societal goal of science. An inscription on the dome of the Great Hall at the National Academy of Sciences beautifully describes the many roles of science and--interestingly--cites this economic role first. It reads. . . "To Science: pilot of industry, conquerer of disease, multiplier of the harvest, explorer of the universe, revealer of nature's law and eternal guide to truth." [Perhaps this reveals something about the practical nature of the culture of 1924 when the inscription was written.]

- o The combining of forces to solve problems and to make maximum use of our resources has a very long history in the United States. One can go back to the Morrill Act of 1862 which provided massive federal support to higher education and gave impetus to scientific farming to create the agricultural industry that today feeds the nation and a good part of the world. One recalls the 1950s when federal support for education and research led to great advances in the physical and engineering sciences, collaboration among government, academia and industry carried us to the moon and beyond and led to knowledge and

technology from which we are still reaping huge social and economic benefits. Fears of negative impact on the freedom and integrity of higher education were voiced then. Cooperation in research and in organizational problem-solving overcame obstacles and brought us successfully into a new era of achievement.

- In 1986 total national support for health R&D was an estimated $14.3 billion. Of that total, 35 percent was supported by NIH, 39 percent by industry, and 26 percent by other federal, state and local governments and private non-profit organizations. (Incidentally, the cross-over year when industry for the first time surpassed NIH in percent of health R&D support was 1983.) But when we look at all basic health research support, which totaled some $3.9 billion, 65 percent was provided by NIH and about 9 percent by industry.

- Breaking down those figures further, by type of effort supported, we find these comparisons: NIH support in 1986 was allocated approximately 62 percent to basic research, 29 percent to applied research and 8 percent to development. Our internal analysis found a different, but anticipated, trend in industry support: 9 percent for basic research, 38 percent for application, and 53 percent for development.

- It is clear, then, that government and academia and industry perform complementary roles in the advancement and application of biomedical knowledge.

- Recent years have seen the establishment of a number of new ties between industrial organizations and some of the nation's leading academic institutions. Many ingenious contractual arrangements have been devised to serve optimally the purposes of the partners while protecting their interests with respect to freedom of inquiry, open scientific communications, and proprietary rights. The NIH has an observational interest in such new partnerships but we have not interposed ourselves in the new arrangements and have no intention of doing so.

- Important links between the NIH and industry were established more than 30 years ago with the establishment of the NIH patent policy in 1953.

- In the extramural programs each grantee institution was given the opportunity to enter an institutional patent agreement. Under the agreement the institutions were encouraged to patent innovations resulting from NIH-supported research and to arrange for the licensing for development and marketing of such innovations. Under the patent agreements the institutions themselves receive a major share of the royalties from such licenses but they must invest such proceeds in further biomedical research. The inventors also receive stated shares. The NIH does not participate in the income from such extramural licensing agreements.

- The NIH patent program provides for promoting the transfer and commercialization of federally-funded inventions by the private sector. Inventions that result from in-house research are reported, evaluated, and submitted for patenting with the assistance of the Office of the General Counsel of the Deparment of Health and Human Services, the funding institute, and the inventor.

- Between 1980 and 1984, 282 invention reports were filed by NIH employees, for example, and of these 73 percent have been patented and 51 percent have been licensed to the private sector. In recent years, an average of 500 inventions have arisen directly from NIH-funded research, leading to the filing of an average of 210 patent applications each year.

- I will turn now to other linkages.

  During the first two decades following World War II, the NIH accepted grant applications from institutions and organizations regardless of their "for-profit" or "non-profit" status. However, in the mid-60s congressional concerns prompted a change in that policy and only not-for-profit organizations were considered to to be eligible for grants. This restrictive policy was abandoned in December 1982 so that applications may now be received, reviewed, and if of sufficient merit awarded to industrial organizations as well as to the traditional grantees. Thus, NIH-funded programs can have access to the creative abilities of the many outstanding scientists employed by industry, and conversely these scientists have access to sources of funding for research projects that might not be appropriate objects of company support. Such grants do not now constitute more than a small fraction of our total portfolio and probably will not increase markedly in the foreseeable future.

- However, a new type of grant was created by the Congress in 1982 through legislation mandating that a specified percentage of the funds of federal research agencies be awarded for research by small business organizations. The NIH Small Business Innovation Research Program funded 445 grants in 1986 for a total of $44.5 million. Such awards are made in stages on the basis of merit evaluations by initial review groups operating in much the same manner at the traditional research study sections assess proposals.

- Before the recent policy alterations with regard to grants were made, another linkage with industry had been strengthened. Prior to the late 1970s, agency policy had not permitted appointment of industry's scientists to our initial review groups, or other scientific advisory bodies. It was perceived that such a policy prevented us from utilizing in our review process the substantial and sometimes rare abilities of scientists employed by for-profit organizations. This policy has now been changed.

intramural research program. Under this arrangement scientists from industry may come to NIH and work side by side with NIH investigators in our on-campus laboratories. The guest workers are not paid, but laboratory space and support are provided. Recent legislation covering "volunteer" workers gives a broad statutory base for such programs.

- In a reciprocal arrangement, NIH scientists are now permitted to engage in so-called "outside activities," such as lecturing at or consulting with industrial organizations and receiving honoraria for doing so. For obvious reasons certain restraints must apply to government employees, and in the case of consultations prior approvals must be secured. These steps will be recognized by those of you who have been following this matter as real progress in strengthening relationships between industry and the NIH for the benefit of the American people.

- Another very important area of NIH-industry collaboration has been in clinical trials, particularly in drug trials. The great expense of this type of research would be prohibitive without industry cooperation. Because of NIH commitment to developing drugs against AIDS, it is expected that many more such collaborations will emerge in the next few years.

- Thus, at different levels there have been increasing interactions--provisions have been made to permit NIH scientists to lecture at and consult with industry, guest investigators from industry may now be accommodated within the NIH's intramural laboratories, and active collaboration between industry and NIH is taking place in a number of ways, including conferences for the direct exchange of scientific information.

- In closing, I would like to turn to the historical theme of linkages between biomedical research and industry. Biotechnology is not a phenomenon of the 1980s--in fact, it has a long history. We sometimes forget the strong linkages between the work of Pasteur and industry. In this connection permit me to read the Encyclopedia Britannica's summation of his work: "Pasteur proved microorganisms cause fermentation and disease; he originated and was the first to use vaccines for rabies, anthrax, and chicken cholera; he saved the wine, beer and silk industries of France and elsewhere; he performed important pioneer work in stereochemistry; he originated pasteurization."

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

Mr. Chairman, it is my privilege to present the President's budget proposal for the National Institutes of Health (NIH) for Fiscal Year 1988 and to report briefly on some of our activities and plans. I continue to be impressed and deeply appreciative of the interest and understanding with which you, your colleagues, and the subcommittee staff deal with matters pertaining to the National Institutes of Health.

We are nearing the mid point of a year-long observance of the centennial of the National Institutes of Health. A year ago, at our appropriation hearings, I gave a brief summary of our plans for centennial activities. I am pleased to report the high level of enthusiasm that has developed among many groups for holding special events and ceremonies to mark the 100th birthday of NIH. Between now and mid-October there is a full schedule of centennial events in Washington, as well as in many other parts of the Nation and overseas.

A consortium of leading pharmaceutical companies and the Howard Hughes Medical Institute is underwriting many of the expenses of the centennial observance, especially the four-part series of one-hour television programs being produced for airing by PBS next fall. The series, tentatively entitled "The Health Century," will tell the fascinating and significant story of the great progress that has been made in human health since the 1880s and the vital role played by biomedical research, notably the contributions made by each of the "partners in discovery," academia, industry and the NIH. We are confident that the centennial events and programs will create a better public understanding of the importance of biomedical research and will cause bright young people now making their career choices to consider the satisfaction and value of biomedical research.

During the past year the National Library of Medicine (NLM) also reached a significant milestone--its 150th birthday. The NLM continues to exercise worldwide leadership in scientific communication and is the central resource of our Nation's biomedical information system.

Since we appeared before this Committee to discuss the budget estimates for FY 1987, the NIH has completed the establishment of a new institute, a new national center, and a major new position, all of which were authorized by the Health Research Extension Act of 1985 (P.L. 99-158).

The National Institute of Arthritis and Musculoskeletal and Skin Diseases was established officially April 8, 1986, and on January 16 of this year, Dr. Lawrence Shulman was appointed as the first director of the new institute. The National Center for

Nursing Research was established April 18, last year. The programs of the NCNR will be directed primarily toward basic and applied research related to patient care, the promotion of health, the prevention of illness, and the understanding of individual family and community responses to acute and chronic illness and disability. Another important addition to the NIH organization is the establishment of the Office for Disease Prevention, and the appointment of Dr. William Friedewald as an NIH Associate Director to head the new office. Dr. Friedewald, who has been at NIH for 20 years, is an outstanding scientist/administrator who will have a major role in promoting disease prevention programs within the NIH.

Mr. Chairman, the budget proposal for FY 1988 once again underlines the importance the NIH attaches to research on the acquired immunodeficiency syndrome (AIDS). The AIDS program at NIH supports basic, applied, preclinical, and clinical research with emphasis on natural history, pathogenesis, vaccine development and treatment. Research on the AIDS virus is the primary focus. A major accomplishment of the AIDS program during the past year was the identification of azidothymidine (AZT) and its early testing in patients with penumocystis carinii pneumonia.

The NIH has launched a new program of basic research in structural biology with emphasis on the development of antiviral substances, especially against the AIDS-causing virus. Our intramural scientists will use the methods of structural biology to characterize the AIDS virus at a molecular level in efforts to develop and modify targeted antiviral drugs. This program will complement similar efforts supported by NIH and planned for implementation at universities and other laboratories throughout the country. It is clear that a successful vaccine development program will depend upon a greatly expanded foundation of basic knowledge concerning the AIDS virus.

The FY 1988 request includes $343.5 million for AIDS research by all components of NIH, an increase of $91.0 million over the FY 1987 appropriation.

Molecular biology has progressed to the point where it is now possible to characterize the genetic material of man, in other words the whole human genome, by obtaining complete information on the location of particular genes as well as the order in which their 3 billion chemical building blocks (called nucleotides) appear. The possible benefits of characterizing the human genome are tantalizing. The new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and of the molecular basis of many inherited and "orphan" diseases. We could gain substantial information on cancer as well as on autoimmune and immune deficiency diseases. An extensive science base would be created of special importance to studies of toxicology and the effects of environmental contaminants; and we would hasten the day when physicians may be able to repair or replace defective genes.

Sentiment in the scientific community at this time favors approaching this massive project through a carefully planned stepwise effort rather than a mass attack. In preparation for

further efforts on the project, we are developing collaborative arrangements with the scientific communities in Europe and Japan, and cooperating with other Federal agencies having interest.

The Administration proposes a long term policy of stable and sustainable support for the NIH. The President's budget seeks $5.8 billion in obligational authority in FY 1987 and 1988. The Administration also proposes a policy of appropriating the total NIH allowance for research project grant commitments at the time that they are incurred.

The key adjustment proposed for FY 1987 by the Administration is to extend the availability of $334 million of FY 1987 funds so that they could be obligated during FY 1988. The proposed carryover would be achieved by awarding 700 of the FY 1987 estimated 6,394 competing research project grants in FY 1988 rather than the current fiscal year, and by reducing the average cost of both competing and noncompeting awards in FY 1987. You may be assured, however, that we are now awarding grants in a manner consistent with the funding levels contained in the FY 1987 appropriation. Should Congress enact this proposal of extended availability, only those projects scheduled to receive awards subsequent to congressional action would have their grants reduced.

The revised budget for FY 1987, that would result from the proposed changes, would fund approximately 19,111 total research project grants, an increase of about 315 from the FY 1986 comparable level. All other NIH mechanisms would be funded in the same amounts as in the original FY 1987 appropriations. This includes funding for 560 centers, an increase of 23 over FY 1986, and 10,867 full-time research trainees, an increase of 485 over FY 1986. The funding for AIDS research, would not be affected by the Administration's proposal to revise the FY 1987 budget.

The President's budget request for FY 1988 includes $5,534 million in new budget authority. With the extended availability of $334 million in FY 1987 funds, the total obligational authority for 1988 would be $5,869 million, which is approximately equal to the level of the revised 1987 budget. The request would support 19,131 total research project grants, about the same number as in the proposal for the current year. New and competing renewal grants under the President's FY 1988 proposal would number 5,709 as compared with 5,654 in the revised 1987 budget, and 6,211 in 1986. The average cost per grant would be about the same as in 1987, $164,000 per award.

The 1988 request for research training, $233 million, would support approximately 10,867 trainees, the same number as in the revised 1987 level--approximately the number recommended by the National Academy of Sciences.

The number of research centers would be the same in 1988 as in 1987, but with a decrease in funding support of $1.4 million from FY '87 to the new figure of $522 million.

In the aggregate, the other NIH research mechanisms, such as other research grants, research contracts, the intramural research

programs, research management and support, and disease control, would be maintained at approximately their FY 1987 comparable funding levels. Two exceptions are the Biomedical Research Support Grant (BRSG) and the Extramural Construction Program; both of which are proposed for elimination in 1988. Because of the continuing interest in investigator-initiated research project grants as the most appropriate form of support and the growing concern over budget constraints, the BRSG program and the Extramural Construction Program must rank as lower priorities when compared with other NIH programs.

As part of the President's biomedical research stability policy, the FY 1988 budget also includes a request for advanced appropriations in the amount of $2,726 million to support the outyear commitments (FY 1989 through 1994) generated by the award of competing research project grants during FY 1988. This approach to grant funding would focus attention on the total project and inform the research community of the total funds available for continuation costs. Provisions are made for modest annual increases of the average costs per grant. The funds for the noncompeting continuations would be awarded on an annual basis, as they are now.

I would be pleased to respond to questions about the budget or other matters pertaining to NIH.

health. For example, genetic engineering has made possible the large-scale production of therapeutically useful substances such as insulin, interferons, interleukins, growth hormone, tissue plasminogen activating factor, and blood factor VIII.

In addition, more than 35 national biomaterials resources in biotechnology are being supported by the NIH. These include banks of cells, cell products, cell fractions, and mutant organisms; archives of germ plasm; collections of DNA probes and libraries; banks of hybridomas; and national databases that provide for searching, analysis, matching, and manipulation of nucleic acid and protein sequences. These are major resources, each underpinned by the research of broad groups of investigators and supported by grant and contract awards from a number of the NIH institutes and divisions.

In response to the flood of laboratory data produced by NIH-supported research, and to aid the scientists who investigate molecular biological phenomena, NIH is funding about a dozen major computerized databases, each with its own characteristics. Some of these are at NIH, others at institutions around the United States and in other countries. Among them are the Hybridoma Data Bank, ATCC Cell/Tumor Bank, the Human Mutant Cell Repository, the Human DNA Probe Repository, Human Gene Library, Protein Information Resource, GenBank,® and the European Molecular Biology Laboratory (EMBL) Bank of Nucleic Acid Sequences.

The subject of biotechnology is of such importance that last year a meeting of the Advisory Committee to the Director, NIH, was devoted to reviewing the NIH's role in the field. Conclusions from that meeting included continued NIH support for basic biomedical research and research training, since this policy has helped earn the United States its preeminent position in the world in the area of biotechnology. In addition, it was suggested that NIH facilitate further developments in biotechnology through cooperative efforts with industry and academia and we have taken steps in this direction.

Another such meeting on a closely related topic focused on "Characterizing the Human Genome," a feat that is feasible because of advances in molecular biology and biotechnology. At this meeting, after a wide-ranging discussion, a number of conclusions were developed. For the purposes of this hearing, two are pertinent.

First, that chromosome mapping and selective DNA sequencing are the best approach to gaining an understanding of the human genome. Second, that information-handling services are absolutely necessary for optimal progress in biotechnology. Not only must new information services be developed and existing information resources expanded, but sophisticated communication linkages must be forged between resources, particularly databanks, so that researchers can have rapid and

efficient access to the totality of scientific information. These tasks are appropriate to the National Library of Medicine, an institution with a long and distinguished history in developing innovative biomedical information services.

In order to coordinate the need for access to such information with the existing resources, I established, earlier this year, a National Biomaterial Resource Committee. The five permanent members of this committee are the NIH Deputy Director (who will chair the committee), the Associate Director for Program Planning and Evaluation, the Associate Director for Administration, the Director of the National Library of Medicine, and the Director of the Division of Research Resources. One-year rotating memberships will be distributed among the Directors of the various other Bureaus, Institutes, and Divisions that constitute NIH. The charge to the committee is to coordinate the entire NIH approach to funding national biomaterial resources.

In conclusion, it is quite clear that support of biomedical research related to biotechnology will remain a subject of the highest priority at the National Institutes of Health. This heavy investment of research funds is entirely appropriate, since the potential of this field for improving human health is enormous. At the same time, we must invest in efforts to

collect, organize, and disseminate biotechnology information. Continued scientific progress demands it.

It is the consensus of those who are familiar with its work that the National Library of Medicine, at NIH, is the logical organization to undertake the building and coordinating of biotechnology information resources in medicine. The Library's pioneering use of computers to organize the world's biomedical literature offers a paradigm of the kind of new systems that must be put in place to deal with the challenges of exchanging and utilizing such biotechnological information. I am pleased that you will have the opportunity today to hear more about the role of the Library in matching the needs of the molecular biologists with the solutions resulting from advances in information science.

Mr. Chairman, members of the Committee, this concludes my prepared statement. I would be happy to answer any questions you would like to ask.

TALKING POINTS FOR HARVARD*
BY
JAMES B. WYNGAARDEN, M.D.**

- I am delighted that I was able to accept Dr. Tosteson's invitation to be here this afternoon for the special Harvard observance of NIH's Centennial.

- As you can imagine, someone representing an institution just 100 years old appears here with a certain humility--generated by my consciousness of the venerability of Harvard, which recently observed its 350th. Even that is comparatively recent history when compared with the 600th anniversary observed by the University of Heidelberg just last year.

- But I am delighted that the Harvard institutions--some of NIH's most prominent "partners in discovery"--have chosen to set aside time to honor the NIH in this way.

- Many of you know something of NIH's history, for example its beginning in a one room attic laboratory on Staten Island, New York. But some milestones bear mentioning:

- In 1891 the Laboratory of Hygiene--as it was then called--moved to Washington, D.C., underscoring the status of the laboratory as a National resource.

- The laboratory was the site of many heroic and successful battles against disease (pellagra, Rocky Mountain Spotted Fever, psittacosis or parrot fever, etc.).

- The Ransdell Act of 1930 was a landmark in our history. It changed the name of the Hygienic Laboratory to the National Institute of Health and expanded its emphasis from a concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention, and cure of disease." Shortly thereafter the agency moved to its present site in Bethesda, Maryland, and was renamed the National Institutes of Health.

- For the first 50 years of its existence, NIH was essentially a free standing laboratory. It was not until World War II that NIH began to forge its relationships with such institutions as Harvard--its academic partners in discovery. This was the dawn of what we call "The Modern NIH".

- Following the war, some 250 war-related medical research projects underway in universities and hospitals were transferred to the NIH.

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* Presentation at Harvard Medical Center in Observance of the NIH Centennial, Boston, Massachusetts, May 6, 1987.

** Director, National Institutes of Health, Bethesda, Maryland.

- The high-level decision to transfer the grants to NIH confirmed our role as the principal biomedical research arm of the Federal Government. It also established grants as a powerful mechanism for the support of such research.

- Since that time NIH has held to a number of principles which serve us well today: Quote from Vannevar Bush: "The publicly and privately-supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge". In 1985, for example, 73 percent of health R&D funds used by universities came from the Federal Government; 23 percent from state, local and nonprofit sources; and only 4 percent from industry.

- From that same period we also date our emphasis on basic research and the conviction that investigator-initiated research into biological processes holds the greatest promise of significant discovery. Another principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health goals in the future. And a final basic tenet is that of accountability--we took care from the beginning that the relationships between the government and academia developed as a real partnership. Hence, our peer review system which in any given year draws upon more than 2,000 outside advisors.

- Many remember the Shannon years of NIH fondly, for that was the period when Dr. James A. Shannon, NIH director from 1955-1968, took these basic principles and brought them to a crescendo. When he became director, the total budget for NIH was $82 million and when he retired, the NIH budget had passed $1 billion.

- Shannon insisted that congressional mandates to conduct research on cancer, heart disease, and arthritis, for example, be interpreted broadly. He realized that the science base did not yet exist to permit a frontal assault on the diseases themselves. He set about building a research capability in this country, both through the intramural program at NIH in Bethesda and through substantial expansion of the mechanisms of grants-in-aid to institutions. During his tenure, the basic mechanisms of support of biomedical science were established, and these have continued to serve us well.

- His corollary objectives included strengthening the institutions in which biomedical research could be done, and development of training mechanisms that would ensure a continuing supply of competent scientists drawn from the best and brightest young people in the universities. Together with the Hill-Burton money for clinical facilities, NIH construction funds for research facilities modified the

topography of the academic medical center, indirectly changing--and greatly strengthening--medical education.

- Since those Shannon years, the challenge has been to make adjustments to changing fiscal climates so that the momentum of scientific discovery is maintained. A mature agency competing with others for precious public funds, NIH has done well, with its budget now at $6.2 billion. Nevertheless, even at that level, we are only funding about a third of approved grants each year.

- Certainly, NIH can take some pride in its role in fostering the biomedical research enterprise largely centered at academic centers. A measure of the success of this endeavor--I think a key accomplishment--has been the fostering of the so-called new biotechnology revolution.

- This enterprise has burgeoned into a billion dollar industry that already can be credited with many advances to help mankind. Promises for the future are incalculable.

- These vast accomplishments and promises are to a great extent the result of steadfast support for basic biomedical research by the NIH.

- For more than 30 years, NIH has funded pioneering investigations and research training in basic sciences--molecular genetics, molecular and cell biology, and immunology--to advance understanding of biological processes in health and disease. As this research began to unfold its potential, NIH extended its support to more focused research projects--manipulating genes, cloning DNA, and creating monoclonal antibodies. In addition, most of the men and women who today are participating in the biotechnology drama were trained by or through NIH. Furthermore, NIH has played a key role in piloting biotechnology's development by taking early responsibility for ensuring the safety of federally-funded research involving recombinant DNA.

- The developments have brought a new member strongly into the biomedical research partnership--industry.

- But probably the most important accomplishment of the NIH--along with its partners in academia and industry--has been the enormous improvement in health status of the American people in the past 40-45 years: for example--improved survival for cancer patients, reduction in mortality from heart disease and stroke, development of effective vaccines, etc. All of these are the direct result of our successful biomedical research enterprise.

- It can be said without hesitation that although the average citizen may never have heard the words "National Institutes of Health" and although the public may not understand how their tax money is invested through the NIH in search of new knowledge, there is not a household in this country that has not been touched by the NIH in some way.

NIH AT THE CENTURY MARK*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM GREATLY HONORED TO HAVE BEEN INVITED TO GIVE THE MEMORIAL LECTURE AT THIS PLENARY SESSION OF THE 1987 MEETING OF THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION. ON BEHALF OF THE NATIONAL INSTITUTES OF HEALTH I ALSO WISH TO TAKE THIS OPPORTUNITY TO EXPRESS OUR APPRECIATION TO THE GOVERNING BOARD OF THE ASSOCIATION FOR THIS RECOGNITION OF THE CENTENNIAL OF THE NIH. YOUR DISTINGUISHED ORGANIZATION AND THE NATIONAL INSTITUTES OF HEALTH FOR MANY YEARS HAVE DEVOTED SUBSTANTIAL EFFORTS AND RESOURCES TO THE SEARCH FOR BETTER UNDERSTANDING OF DIGESTIVE DISEASES, A MAJOR HEALTH PROBLEM IN THIS COUNTRY.

BOTH OF OUR ORGANIZATIONS HAD THEIR BEGINNINGS IN THE LATE NINETEENTH CENTURY, THE AGA IN 1897 AND THE NIH IN 1887. IT WAS A TIME OF GENERAL FERMENT IN THE SCIENCES. THE 1880's AND THE 1890's WERE YEARS IN WHICH A RAPID EXPANSION OF KNOWLEDGE WAS OPENING UP NEW AREAS OF HUMAN ENDEAVOR. IT WAS A TIME OF SOLID SCIENTIFIC ADVANCES, PARTICULARLY IN BIOLOGY, CHEMISTRY AND PHYSICS. BEING INVOLVED IN MANY DIFFERENT CENTENNIAL OBSERVANCES HAS SENSITIZED ME TO SUCH ANNIVERSARIES, SO THAT I HAVE NOTICED A NUMBER OF OTHER ORGANIZATIONS AND GROUPS THAT CAME INTO EXISTENCE IN 1887 AS DID NIH. IN LATER MARCH IT WAS MY PLEASURE, FOR EXAMPLE, TO REPRESENT THE NIH AS A PARTICIPANT IN A JOINT CENTENNIAL OBSERVANCE WITH THE AMERICAN PHYSIOLOGICAL SOCIETY. ON MAY 26 IT WILL BE MY PRIVILEGE TO OPEN A JOINT SYMPOSIUM TO BE HELD ON OUR CAMPUS IN BETHESDA HONORING THE PASTEUR INSTITUTE, WHICH ALSO IS CELEBRATING ITS CENTENNIAL IN 1987.

IT IS ALSO OF INTEREST TO NOTE THAT HOLLYWOOD'S 100TH BIRTHDAY IS BEING CELEBRATED THIS YEAR, BUT AS FAR AS I KNOW, WE HAVE NO PLANS FOR JOINT ENDEAVORS.

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NOTWITHSTANDING THE FACT THAT THE NIH WAS ESTABLISHED IN THE SAME YEAR AS THE PASTEUR INSTITUTE, 1887 WAS A TIME WHEN MEDICAL SCIENCE IN THE UNITED STATES LAGGED FAR BEHIND THE STATE OF KNOWLEDGE IN EUROPE. STUDIES IN THE NEW DISCIPLINE, BACTERIOLOGY, LED BY ROBERT KOCH AND LOUIS PASTEUR, WERE BEING CARRIED OUT IN INCREASING NUMBERS IN EUROPEAN LABORATORIES, BUT FEW AMERICANS WERE PARTICIPATING IN THIS RESEARCH EITHER AT HOME OR ABROAD.

IN A FASCINATING BOOK ON THE AMERICAN SCIENTIFIC EXPERIENCE WITH CHOLERA, W. E. VAN HEYNINGEN AND THE LATE JOHN R. SEAL REPRINTED A CARTOON FROM THE AUGUST 2, 1883, ISSUE OF THE ORIGINAL LIFE MAGAZINE. IN THE FOREGROUND OF THE DRAWING A ROMAN SOLDIER, LABELED "SCIENCE," SAT SLEEPING AT HIS GUARD POST, DOCK AT THE PORT OF NEW YORK. LOOMING OVER THE GUARD, AND ABOUT TO POUNCE WAS A GHASTLY SPECTRE LABELED "CHOLERA" ARISING FROM A DISTANT CITY ACROSS THE OCEAN. THE CAPTION FOR THE CARTOON PROVIDES A NUGGET OF NIH HISTORY. REFERRING TO THE SLEEPING SENTINEL, THE AUTHORS EXPLAINED, "AMERICAN MEDICAL SCIENCE DID NOT SLUMBER IN 1883, IT HARDLY EXISTED." THEY ADDED, "THE CONCERN IN AMERICA ABOUT IMPORTATION OF THE FIFTH CHOLERA PANDEMIC OF 1881 SENT YOUNG DR. JOSEPH KINYOUN TO STUDY WITH PASTEUR AND KOCH IN EUROPE. RETURNING, HE SET UP A BACTERIOLOGICAL LABORATORY IN THE MARINE HOSPITAL, STATEN ISLAND, N.Y., IN 1887. THE AUTHORS WENT ON TO NOTE THAT, "THE PRESENT NATIONAL INSTITUTES OF HEALTH IS DIRECTLY TRACEABLE TO THAT LABORATORY."[1]

FIRST CALLED THE LABORATORY OF HYGIENE, AND LATER THE HYGIENIC LABORATORY, THIS MODEST FACILITY WAS MOVED TO WASHINGTON IN 1891 WHERE IT OCCUPIED A FLOOR OF AN EXISTING GOVERNMENT BUILDING ON CAPITAL HILL KNOWN AS THE BUTLER BUILDING. THE MOVE TO WASHINGTON WAS A SIGNIFICANT STEP IN THAT IT WAS TAKEN IN RECOGNITION OF THE NEED FOR THE LABORATORY IN A BROADER ROLE THAN THAT OF SUPPORT FOR QUARANTINE ACTIVITIES. IT BEGAN TO BE SEEN AS A NATIONAL RESOURCE.

IN 1904 THE HYGIENIC LABORATORY WAS MOVED TO NEWLY CONSTRUCTED BUILDINGS NEAR WHAT IS NOW THE KENNEDY CENTER. THE NEW BUILDINGS BECAME THE HOME OF NIH FOR 35 YEARS. IT WAS IN THIS PERIOD AND IN THESE LABORATORIES AND OFFICES THAT STRATEGY AND TACTICS WERE DEVELOPED FOR SUCCESSFUL BATTLES AGAINST SUCH DISEASES AS TYPHUS AND PELLAGRA.

AMONG THE SCIENTISTS ASSOCIATED WITH THE HYGIENIC LABORATORY WERE SOME OF THE HEROES OF MEDICINE. FOR EXAMPLE, DR. HOWARD TAYLOR RICKETTS, WHOSE WORK ON ROCKY MOUNTAIN SPOTTED FEVER PROVIDED THE KEY FOR FINDING THE CAUSE OF EPIDEMIC TYPHUS. RICKETTS DIED OF TYPHUS IN 1910, A VICTIM OF THE ORGANISM HE HAD EARLIER DESCRIBED AND THAT SUBSEQUENTLY WAS NAMED FOR HIM--THE RICKETTSIA.

A GIANT AMONG THE REMARKABLE MEMBERS OF THE STAFF OF THE HYGIENIC LABORATORY WAS DR. JOSEPH GOLDBERGER. CONSIDERED TO BE ONE OF THE MOST PROMISING OF THE YOUNG MEN CONNECTED WITH THE HYGIENIC LABORATORY, HE WAS PLACED IN CHARGE OF THE PUBLIC HEALTH SERVICE INVESTIGATION OF PELLAGRA, THEN PREVALENT IN THE SOUTH, BUT A PROBLEM IN 40 STATES AS WELL AS THE DISTRICT OF COLUMBIA MOST MEDICAL SCIENTISTS OF THE TIME THOUGHT PELLAGRA WAS CAUSED BY A PARTICULAR ORGANISM. DR. GOLDBERGER ARGUED THAT IF A BACCILUS WERE THE CAUSE, SOME OF THE DOCTORS AND NURSES AND OTHER ATTENDANTS WORKING AROUND THE PELLAGRA PATIENTS DAILY WOULD GET IT TOO. HE POINTED OUT THAT THE ONE DIFFERENCE BETWEEN THE INMATES IN PRISONS AND MENTAL INSTITUTIONS AND THE PEOPLE WHO CARED FOR THEM WAS THEIR DIET--YET MANY OF THE INMATES SUFFERED FROM PELLAGRA, THEIR ATTENDANTS DID NOT.

DR. GOLDBERGER'S CONFIRMATORY INVESTIGATION WAS A CLASSIC OF EPIDEMIOLOGY. HE AND HIS ASSOCIATES SHOWED THAT THE POOR, MONOTONOUS DIETS COMMON TO MANY LOW-INCOME PEOPLE--DIETS HIGH IN CARBOHYDRATE AND LOW IN GOOD QUALITY PROTEIN AND FRESH VEGETABLES--INDUCED PELLAGRA WHEN FED TO CONVICT VOLUNTEERS IN A MISSISSIPPI PENITENTIARY. IN OTHER PUBLIC INSTITUTIONS WHERE THE DISEASE OCCURRED, THESE INVESTIGATORS DEMONSTRATED THAT GENEROUS AMOUNTS OF MILK, EGGS, MEAT, BEANS, AND PEAS PREVENTED IT. STILL, PHYSICIANS WHO WERE TREATING PELLAGRA STRONGLY BELIEVED THAT IT WAS DUE TO AN INFECTIOUS ORGANISM AND WOULD NOT ACCEPT GOLDBERGER'S EVIDENCE.

AS A FINAL PROOF THAT NO INFECTIOUS ORGANISM WAS INVOLVED, GOLDBERGER AND ONE OF HIS COLLEAGUES INJECTED EACH OTHER WITH BLOOD FROM A PELLAGRA PATIENT. LATER, GOLDBERGER AND FOUR ASSOCIATES SWALLOWED CAPSULES CONTAINING PATIENTS' WASTES AND SKIN SCRAPINGS, AND GOLDBERGER INJECTED BLOOD FROM A PELLAGROUS WOMAN INTO HIS WIFE, MARY. NONE CONTRACTED THE DISEASE, THOUGH IT IS NOT RECORDED WHAT ADVERSE SYMPTOMS MAY HAVE RESULTED FROM THESE BRAVE EXPERIMENTS.

GOLDBERGER LATED DEVELOPED A TREATMENT USING YEAST IN THE DIET AND SHOWED THAT THE AMINO ACID TRYPTOPHAN WAS CRUCIALLY RELATED TO THE CAUSE OF THE DISEASE. SOON THE B VITAMIN NICOTINIC ACID, NOW CALLED NIACIN, WAS IDENTIFIED AS A SPECIFIC PELLAGRA PREVENTIVE. FROM THESE BEGINNINGS AN INTEREST IN OTHER ASPECTS OF NUTRITION EVOLVED, PARTICULARLY IN THE NIH COMPONENT NOW KNOWN AS THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES.

AN IMPORTANT EVENT IN THE CHRONOLOGY OF THE DEVELOPMENT OF NIH OCCURRED IN 1930. IT WAS IN THAT YEAR THAT THE RANSDELL ACT WAS PASSED, CHANGING THE NAME OF THE HYGIENIC LABORATORY TO THE NATIONAL INSTITUTE OF HEALTH AND EXPANDING THE SCOPE OF ITS LEGISLATIVE MANDATE FROM ITS FORMER CONCENTRATION ON INFECTIOUS DISEASES (OR WHAT WERE THOUGHT TO BE INFECTIOUS) TO THE BROADER ASSIGNMENT OF "....ASCERTAINING THE CAUSE, PREVENTION AND CURE OF DISEASE."

THE CRUCIAL CHANGE, HOWEVER, THAT HERALDED AS WELL AS CREATED THE "MODERN NIH," TOOK PLACE AT THE END OF WORLD WAR II WHEN THE WARTIME OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT (OSRD), THEN GOING OUT OF EXISTENCE, TURNED OVER TO THE NIH RESPONSIBILITY FOR THE COMPLETION OF SOME 250 MEDICAL RESEARCH PROJECTS BEING CONDUCTED AS A PART OF THE WAR EFFORT AT UNIVERSITIES, MEDICAL SCHOOLS, HOSPITALS AND PHARMACEUTICAL LABORATORIES. THIS HIGH-LEVEL DECISION TO TRANSFER ADMINISTRATION OF THE GRANTS TO NIH NOT ONLY CONFIRMED THE AGENCY'S ROLE AS THE PRINCIPAL BIOMEDICAL RESEARCH ARM OF THE FEDERAL GOVERNMENT, IT ALSO ESTABLISHED EXTRAMURAL GRANTS AS THE DOMINANT MECHANISM FOR THE SUPPORT OF SUCH RESEARCH.

THE TRANSFER OF THE FUNDS FROM THE OSRD INVOLVED LESS THAN $1 MILLION, BUT THE EVENT MARKED THE BEGINNING OF THE MODERN NIH THAT CURRENTLY FUNDS SOME 20,000 GRANTS AT AN ANNUAL COST OF NEARLY $5 BILLION.

INCREASES IN THE NIH BUDGET HAVE BEEN SPECTACULAR SINCE THE ADDITION OF THE EXTRAMURAL DIMENSION TO ITS PROGRAMS. MEASURED IN CONSTANT DOLLARS THE TOTAL BUDGET OF THE NIH GREW AT AN ASTOUNDING AVERAGE RATE OF 24 PERCENT PER YEAR FOR MORE THAN 20 YEARS FORM 1945 TO 1968. SINCE THAT TIME THE GROWTH PER YEAR HAS BEEN AT A SLOWER RATE, 22 PERCENT A YEAR, BUT IN THE PAST FIVE YEARS THERE HAS BEEN A STEEPENING OF THE GROWTH CURVE TO ALMOST 6 PERCENT PER YEAR. THE FY 1987 APPROPRIATION FOR THE NIH IS $6.18 BILLION, THE HIGHEST EVER. OUR 1988 BUDGET IS NOW UNDER CONSIDERATION BY THE CONGRESS, WHICH, BY THE WAY, I CANNOT RESIST NOTING IS THE 100TH CONGRESS.

THE RAPID EXPANSION OF THE NIH ORGANIZATION HAS MIRRORED PUBLIC CONCERN ABOUT SPECIFIC DISEASES AND GENERAL CATEGORIES OF HEALTH PROBLEMS. THE NAMES OF THE TWELVE INSTITUTES CONSTITUTE A KIND OF HISTORICAL CATALOG. FROM THE BEGINNING, HOWEVER, THE NIH HAS PLACED STRONG EMPHASIS ON THE CONDUCT AND SUPPORT OF BASIC RESEARCH, AND OUR COMMITMENT TO BASIC RESEARCH HAS BEEN SUSTAINED OVER THE YEARS. IN FACT, IT HAS GROWN STRONGER. SOME 30 TO 35 PERCENT OF OUR BUDGET WAS EXPENDED FOR BASIC RESEARCH IN 1970. BY 1980 BASIC RESEARCH CONSTITUTED 52 PERCENT, AND BY 1986 IT AMOUNTED TO 63 PERCENT OF THE TOTAL PEER REVIEW. THIS RAPID INCREASE IS PARTLY DUE TO THE PRIORITY WE HAVE GIVEN INVESTIGATOR-INITIATED GRANTS AND PARTLY TO THE CURRENT DECLINE IN THE USE OF CONTRACTS FOR THE SUPPORT OF RESEARCH. IT ALSO IS AN INDICATION OF THE ACCELERATED RATE OF DISCOVERY IN ALL ASPECTS OF MOLECULAR BIOLOGY.

AT THE BEGINNING OF MY REMARKS I TOLD HOW DEEPENING CONCERN ABOUT IMPORTING CHOLERA INTO THIS COUNTRY HAD PROVIDED THE IMPETUS FOR SELECTING DR. KINYOUN FOR ADVANCED TRAINING AND ESTABLISHMENT OF THE LABORATORY OF HYGIENE. IN 1887 AND 1888 DR. KINYOUN WAS SUCCESSFUL IN ISOLATING VIBRO CHOLERA FROM IMMIGRANTS, BUT STRICT QUARANTINE WAS CREDITED WITH PREVENTING ITS ENTRY. BEYOND DETECTING WHAT APPEARED TO BE THE CAUSATIVE AGENT, PROGRESS IN UNDERSTANDING THE DISEASE WAS PAINFULLY SLOW. IT TOOK 75 YEARS FOR ROBERT KOCH'S SUGGESTION THAT CHOLERA WAS A POISONING TO BE VERIFIED. THE TOXIN WAS NOT FOUND UNTIL 1959. DURING THE INTERIM THERE WERE MANY DIVERSIONS THAT OBSCURED THE DEBATE ON THE PATHOGENESIS OF CHOLERA AND THE ROLE OF THE TOXIN. ONE OF MY LONG-TIME FRIENDS, THEN A JUNIOR SCIENTIST AT THE NIH, THE LATE ROBERT GORDON, PARTICIPATED IN RESEARCH THAT CLEARED AWAY SOME OF THE CONFUSION. BOB GORDON'S WORK ON CHOLERA PROVIDED AN EXAMPLE OF NIH'S INVOLVEMENT ACROSS THE BASIC AND CLINICAL RESEARCH SPECTRUM.

HE DEVELOPED A DIAGNOSTIC TEST USING RADIOACTIVE POLYVINYLPYRROLIDONE WHICH MADE POSSIBLE THE RECOGNITION OF DISEASES IN WHICH THERE IS A LOSS OF PROTEIN IN THE DIGESTIVE SYSTEM. HIS DEMONSTRATION THAT THE LARGE MOLECULES OF THIS DIAGNOSTIC AGENT DID NOT LEAK INTO THE GUT IN CHOLERA FINALLY PUT AN END TO THE HYPOTHESIS THAT THE STRIPPING OF THE INTESTINAL EPITHELIUM WAS THE CAUSE OF THE PRODIGIOUS LOSS OF FLUID IN CHOLERA.

DURING A VERY PRODUCTIVE THREE-YEAR ASSIGNMENT IN DACCA AS CHIEF OF CLINICAL RESEARCH AT THE SEATO CHOLERA RESEARCH LABORATORY, DR. GORDON HEAD AN INTERNATIONAL RESEARCH GROUP THAT DEMONSTRATED THE EFFECTIVENESS OF A COORDINATED RESEARCH EFFORT, IN FIGHTING ONE OF THE LAST MAJOR EPIDEMIC DISEASES AFFLICTING MANKIND. DURING THE COURSE OF A SEVERE CHOLERA EPIDEMIC IN DACCA, 150 PATIENTS WERE ADMITTED TO HIS LABORATORY'S 20-BED EXPERIMENTAL WARD IN TWO WEEKS TIME. THIRY-FIVE ARRIVED IN ONE DAY, 20 IN ONE HOUR. DR. GORDON AND HIS STAFF WORKED CONTINUOUSLY NIGHTS AND WEEKENDS TREATING VICTIMS, MANY OF WHOM SLEPT ON THE FLOOR BECAUSE OF THE LACK OF BEDS. ALTHOUGH THE WARD'S FACILITIES WERE SEVERELY TAXED, ALL OF THE PATIENTS RECOVERED. RESEARCH DURING THE COURSE OF THE TREATMENT DEMONSTRATED THAT, FOR EXAMPLE, BY ADDING ANTIBACTERIAL DRUGS, SPECIFICALLY TETRACYCLINE, TO THE BASIC THERAPEUTIC REGIMEN OF ORAL REHYDRATION, IT WAS POSSIBLE TO SHORTEN THE COURSE OF CHOLERA.

DURING HIS TENURE AS CLINICAL DIRECTOR OF THE OLD NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM AND DIGESTIVE DISEASES, DR. GORDON'S SKILL IN CHOOSING CAPABLE YOUNG CLINICAL ASSOCIATES AND STIMULATING THEM TO DO THEIR BEST ILLUSTRATES ANOTHER CRITICALLY IMPORTANT ASPECT OF NIH PROGRAMS--RESEARCH TRAINING.

FROM THE PERSPECTIVE OF THE CENTURY MARK, IT IS CLEAR THAT THE IDEAS, TECHNIQUES, AND RESEARCH FINDINGS DEVELOPED OVER THE LAST CENTURY BY GRANT-SUPPORTED AND INTRAMURAL SIENTISTS HAVE IMPROVED OUR UNDERSTANDING AND ABILITY TO TREAT DIGESTIVE DISEASES. FOR EXAMPLE, TECHNOLOGICAL ADVANCES IN THE DEVELOPMENT AND USE OF ENDOSCOPIC DEVICES HAVE FACILITATED THE DIAGNOSIS AND DETECTION OF MANY DIGESTIVE DISEASES.

FIBEROPTIC ENDOSCOPY ENABLES A PHYSICIAN TO SEE THE UPPER CASTROINTESTINAL TRACT AND REMOVE COLONIC POLYPS AND COMMON BILE DUCT GALLSTONES WITHOUT SURGERY. LASER ENDOSCOPY HAS CREATED THE ABILITY TO STOP BLEEDING IN THE GASTROINTESTINAL TRACT AND TO DESTROY INTESTINAL CANCERS IN PATIENTS WHO WOULD NOT HAVE BEEN TREATED WITH SURGERY. VIDEO ENDOSCOPY PERMITS PHYSICIANS TO RECORD AN ENDOSCOPIC PRODEDURE AND PLAY BACK THE TAPE WITHOUT INVOLVING THE PATIENT IN ADDITIONAL EXAMINATIONS. THROUGH THE USE OF SATELLITE TRANSMISSIONS, CONSULTING PHYSICIANS IN DISTANT LOCATIONS CAN VIEW A PROCEDURE ALMOST INSTANTLY.

THE TOTAL NIH INVESTMENT IN RESEARCH ON DIGESTIVE DISEASES HAS INCREASED BY 27 PERCENT SINCE 1984. DURING THE CURRENT FISCAL YEAR NIH FUNDING FOR THE CONDUCT AND SUPPORT OF RESEARCH ON DIGESTIVE DISEASES WILL TOTAL $205 MILLION. SEVEN OF OUR RESEARCH INSTITUTES AND THE DIVISION OF RESEARCH RESOURCES ARE INVESTING SUBSTANTIAL AMOUNTS RANGING FROM OVER A MILLION BY THE NATIONAL INSTITUTE ON AGING TO OVER 486 MILLION BY THE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES.

IN REVIEWING THE DIGESTIVE DISEASES PROGRAM ACTIVITIES OF THE SEVERAL COMPONENTS OF NIH, I NOTED A NUMBER OF REFERENCES TO MOLECULAR BIOLOGY, AN AREA OF EXPLOSIVE SCIENTIFIC ACTIVITY THAT HAS PROVIDED MAJOR INSIGHTS INTO THE GENETIC CONTROL OF THE FUNCTIONS OF PROTEINS CELLS, AND ORGANS. SUCH ADVANCES PROVIDE EFFECTIVE NEW TOOLS AND TECHNIQUES THAT CAN ACCELERATE ACQUISITION OF KNOWLEDGE ABOUT CAUSES AND PREVENTION OF DIGESTIVE DISEASES.

AS WE CONSIDER WHAT THE SECOND CENTURY WILL BRING IN ALL AREAS OF NIH CONDUCTED AND SUPPORTED BIOMEDICAL RESEARCH, IT SEEMS CERTAIN THAT MOLECULAR BIOLOGY AND ITS RELATED DISCIPLINES WILL PLAY A MAJOR ROLE.

HISTORIANS OF SCIENCE WILL PROBABLY SAY THAT THE MOST SIGNIFICANT CONTRIBUTION OF THE NIH THUS FAR HAS BEEN THE SUPPORT OF PIONEERING WORK IN MOLECUALR BIOLOGY THAT BEGAN TO FLOWER IN THE 1950s AND CONTINUES UNABATED. THIS RESEARCH HAS LED TO A VIRTAL EXPLOSION EXTENDING ACROSS ALL BIOLOGICAL SCIENCES. IT IS THE FOUNDATION FOR THE RECOMBINANT DNA TECHNIQUE WHOSE POSSIBILITIES ARE ONLY BEGINNING TO BE REALIZED. AN ENTIRELY NEW BIOTECHNOLOGY INDUSTRY IS BASED ON THE RECOMBINANT DNA DISCOVERIES.

AS SCIENCE HAS GROWN MORE SOPHISTICATED IN RECENT DECADES AND HAS BEGUN TO FOCUS ON PROBLEMS OF INCREASING COMPLEXITY, COLLABORATION HAS GROWN BETWEEN SCIENTISTS FROM VARIOUS DISCIPLINES. THIS MOVEMENT TOWARD MULTIDISCIPLINARY RESEARCH HAS FOSTERED COMMUNICATIONS BETWEEN SCIENTIFIC DISCIPLINES AND HAS PROVIDED PROMISING APPROACHES TO RESEARCH PROBLEMS THAT EARLIER HAD REMAINED INTRACTABLE.

TWELVE DIGESTIVE DISEASE RESEARCH CENTERS ARE FUNDED BY THE NIDDK TO ENHANCE THE EFFECTIVENESS OF GROUPS OF RESEARCH SCIENTISTS WHO STUDY DIGESTIVE DISEASES AND DISORDERS. THESE CENTERS ARE LOCATED ACROSS THE UNITED STATES, AND EACH BRINGS TOGETHER BASIC SCIENTISTS, SUCH AS MOLECULAR BIOLOGISTS AND BIOCHEMISTS, AND CLINICIANS SUCH AS INTERNISTS, SURGEONS, ENDOSCOPISTS AND

RADIOLOGISTS. THESE CENTERS MAKE POSSIBLE COOPERATIVE RESEARCH AMONG SUCH INVESTIGATORS BY MAKING CENTRALIZED RESOURCES AMONG SUCH INVESTIGATORS BY MAKING CENTRALIZED RESOURCES READILY AVAILABLE AND BY ENCOURAGING SCIENTISTS TO DEVELOP NEW APPROACHES TO INVESTIGATIONS AND RESEARCH COLLABORATIONS IN THE AREA OF DIGESTIVE DISEASES.

TECHNOLOGICAL ADVANCES IN AREAS SUCH AS X-RAY CRYSTALLOGRAPHY AND MAGNETIC RESONANCE IMAGING PROVIDE NEW OPPORTUNITIES TO INVESTIGATE THE STRUCTURAL PROPERTIES OF PHYSIOLOGICALLY ACTIVE MOLECULES. ONE OF THE MOST RAPIDLY EVOLVING RESEARCH TOOLS IS MAGNETIC RESONANCE IMAGING SPECTROSCOPY. USING THIS TECHNIQUE IT IS POSSIBLE TO DETERMINE THE CHEMICAL COMPOSITION OF BIOLOGICALLY IMPORTANT MOLECULES, THE LENGTH AND NATURE OF THE BONDS HOLDING THE ATOMS OF THE MOLECULES TOGETHER, AND THE THREE-DIMENSIONAL ARRANGEMENT OF THESE MOLECULES. A SIGNIFICANT ADVANTAGE OF THIS TECHNIQUE IS THAT STUDIES CAN NOW BE PERFORMED ON MOLECULES IN THEIR TYPICAL PHYSIOLOGICALLY ACTIVE STATE, THAT IS, EITHER WITHIN THE LIVING ORGANISM OR IN AN AQUEOUS SOLUTION RATHER THAN IN AN UNNATURAL SOLID STATE.

THESE ADVANCES ARE REMINDERS OF WHAT NOBELIST CHRISTIAN DE DUVE HAS DESCRIBED AS "THE CRUCIAL ROLE OF INSTRUMENTS AND TECHNIQUES IN THE PROGRESS OF SCIENCE. NOT THAT THE CREATIVE FACULTIES OF INTELLECT, INTUITION, IMAGINATION, SOMETIMES EVEN GENIUS, MAY NOT BE OF CRITICAL SIGNIFICANCE AT SOME STAGE, BUT," DE DUVE WENT ON THE SAY, "THESE FACULTIES ARE POWERLESS WITHOUT THE MEANS OF ESTABLISHING CONTACT WITH REALITY."[2]

THE PROMISE OF THE VARIOUS NEW APPROACHES TO DRUG DEVELOPMENT HAS LED NIH TOWARD A SPECIAL INITIATIVE TO DEVELOP TARGETED ANTIVIRAL COMPOUNDS, PARTICULARLY FOCUSED ON AIDS. IT IS EXPECTED THAT THESE EFFORTS WILL BRING TOGETHER MULTIDISCIPLINARY TEAMS OF SCIENTISTS IN SUCH AREAS AS X-RAY CRYSTALLOGRAPHY, MAGNETIC RESONANCE IMAGING, MOLECULAR MODELING, DRUG DESIGN, AND SYNTHESIS, AND VIROLOGY. AS YOU KNOW, THE GASTROINTESTINAL TRACT OFTEN SERVES AS THE PRIMARY POINT OF ENTRY FOR THE AIDS VIRUS INTO THE BLOODSTREAM AS WELL AS IN THE PATHOGENESIS OF "SLIM DISEASE" AS A FREQUENT MANIFESTATION OF AIDS IN AFRICA. THUS, RESEARCH ON DIGESTIVE DISEASES PLAYS A CRUCIAL ROLE IN OUR EFFORTS TO CONQUER THIS SCOURGE.

IN THE YEARS PAST A NUMBER OF GENETIC DISEASES--PARTICULARLY INBORN ERRORS OF METABOLISM--YIELDED TO SCIENTISTS USING BIOCHEMICAL METHODS TO IDENTIFY THE DEFECTIVE GENE PRODUCT, SUCH AS A FAULTY PROTEIN. THEY THEN WORKED BACK TO THE MOLECULAR BASIS OF THE DISORDER, SUCH AS THE REPLACEMENT OF ONE AMINO ACID BY ANOTHER. THE DNA ERROR THAT PRODUCED THE AMINO ACID REPLACEMENT COULD THEN BE INFERRED.

NOW, THANKS TO THE SCIENCE OF MOLECULAR GENETICS IT IS POSSIBLE TO IDENTIFY THE GENE AT FAULT WITHOUT IDENTIFYING THE PRIMARY GENE PRODUCT OR THE BASIC BIOCHEMICAL MECHANISM OF THE DISEASE. THE SO-CALLED "NEW GENETICS" MAKES IT THEORETICALLY POSSIBLE TO DIAGNOSE ANY DISORDER THAT CAN BE LINKED TO A DNA POLYMORPHISM IN A FAMILY.

THIS ABILITY WAS FIRST RECOGNIZED IN 1978 WHEN KAN AND DOZY DETECTED SICKLE CELL DISEASE BY OBSERVING THE DNA VARIATIONS THAT WERE INHERITED TOGETHER WITH THE PRESENCE OR ABSENCE OF THE SICKLE CELL GENE WITHIN FAMILIES. RESEARCHERS ARE NOW DISCOVERING SO MANY OTHER RESTRICTION FRAGMENT LENGTH POLYMORPHISMS (RFLPS) THAT, IN ANY FAMILY, IT IS LIKELY THAT A GIVEN GENE DEFECTED CAN BE LOCATED.

LOCALIZATION OF THE RESPONSIBLE GENES HAS BEEN ACCOMPLISHED FOR CYSTIC FIBROSIS, WILSON'S DISEASE, HUNTINGTON'S DISEASE, DUCHENNE MUSCULAR DYSTROPHY, RETINOBLASTOMA, AND ALZHEIMER'S DISEASE. THESE GENE MARKERS ARE ALREADY PROVING USEFUL IN THE CLINIC FOR GENETIC COUNSELIING.

TO AID SCIENTISTS WORKING IN RELATED AREAS, THE NIH HAS FUNDED RECENTLY A DNA DEPOSITORY TO COLLECT, CATALOG, AND DISSEMINATE HUMAN DNA SEGMENTS TO BE USED AS GENE PROBES. USING SUCH TECHNIQUES AS IN SITU HYBRIDIZATION AND CELL FUSION, THE POSSIBILITY OF MAPPING THE ENTIRE HUMAN GENOME IS APPROACHING REALITY.

MOLECULAR BIOLOGY HAS PROGRESSED TO THE POINT WHERE IT IS NOW POSSIBLE TO CHARACTERIZE THE HUMAN GENOME BY OBTAINING COMPLETE NUCLEOTIDE SEQUENCES OF ITS THREE BILLION COMPONENTS. THIS NEW KNOWLEDGE WOULD GREATLY ENHANCE OUR UNDERSTANDING OF THE MOLECULAR MECHANISMS THAT CONTROL GENE EXPRESSION AND THE MOLECULAR BASES FOR INHEITED DISEASE; WE WOULD GAIN SUBSTANTIAL NEW INFORMATION ON NEOPLASTIC AND MALIGNANT DISORDERS AS WELL AS ON AUTOIMMUNE AND IMMUNODEFICIENCY DISEASES. THE INFORMATION TO BE GAINED FROM CHARACTERIZING THE HUMAN GENOME WOULD CREATE AN EXTENSIVE NEW SCIENCE BASE OF SPECIAL

IMPORTANCE TO STUDIES OF TOXICOLOGY AND THE EFFECTS OF ENVIRONMENTAL CONTAMINANTS, AND THE POTENTIAL FOR EFFECTIVE GENE THERAPY WOULD BE ENHANCED.

IT IS CLEAR THAT THE TECHNOLOGY EXISTS FOR COMPLETING A MAJOR PORTION IF NOT ALL OF THE TASK. THERE IS GENERAL CONFIDNCE THAT THE NECESSARY IMPROVEMENTS IN METHODOLOGY WILL BE DEVELOPED TO DEAL WITH CERTAIN PROBLEM AREAS AND THUS MAKE POSSIBLE THE TOTAL CHARACTERIZATIONS.

THE NIH HAS MADE FOUR DECISIONS WITH REGARD TO MAPPING AND SEQUENCING THE HUMAN GENOME:

(1) MAJOR PROBLEMS WITH INFORMATION HANDLING MUST BE SOLVED. THE NIH-SUPPORTED GENBANK--A REPOSITORY FOR NUCLEIC ACID SEQUENCES--HAS ALREADY GROWN 25 FOLD IN THE SHORT TIME IT HAS BEEN IN OPERATION, AND THE GENOME PROJECT WOULD CALL FOR THE HANDLING AND STORAGE OF 1,000 TIMES AS MUCH INFORMATION AS IS CURRENTLY BEING PROCESSED.

(2) THERE IS ROOM FOR CONSIDERABLE IMPROVEMENT IN METHODS FOR CUTTING, PURIFYING AND CLONING DNA FRAGMENTS, AND FOR MAPPING AND SEQUENCING.

(3) THERE IS GREAT INTEREST IN ACCELERATING THE MAPPING AND SEQUENCING OF PARTICULAR GENES THAT ARE OF CLINICAL IMPORTANCE. THIS IS BEING DONE WITH THE USUAL NIH RESEARCH SUPPORT MECHANISMS.

(4) IT IS EARLY TO EMBARK ON A MASSIVE PROGRAM BECAUSE AUTOMATED INSTRUMENTS NOW ON THE HORIZON HOLD OUT THE PROSPECT OF REDUCING THE ULTIMATE COST OF A MAPPING PROJECT BY AN ORDER OF MAGNITUDE OR MORE.

I HAVE MENTIONED A FEW POSSIBILITIES THAT ARE IN THE FOREGROUND AND SOME THAT ARE ON THE HORIZON OF OUR VIEW FROM NIH AT THE CENTURY MARK. AS WE THINK ABOUT THE YEAR AHEAD, IT IS INSTRUCTIVE TO CONSIDER TWO DIFFERENT EVALUATIONS OF THE PRESENT, BOTH OF WHICH ARE SUGGESTIVE OF A PRODUCTIVE FUTURE. THE FIRST, IS FROM NOBELIST DE DUVE WHO, AFTER ADMITTING THE DIFFICULTY OF JUDGING ONE'S OWN TIME, WENT ON TO SAY "....ONE CANNOT HELP THE FEELING THAT THE SECOND HALF OF THIS CENTURY WILL BE REMEMBERED FOR ONE OF THE GREAT BREAKTHROUGHS OF HUMAN KNOWLEDGE--PERHAPS THE GREATEST TO DATE, AS IT CONCERNS THE BASIC MECHANISMS OF LIFE."[3]

THE OTHER QUOTATION IS IN A SOMBER KEY BUT IT SUGGESTS THE FUNDAMENTAL CHALLENGE OF THE NEXT CENTURY. IT IS A COMMENT BY LEWIS THOMAS, WHO OBSEVED, "IN NO OTHER-CENTURY IN OUR BRIEF EXISTENCE HAVE HUMAN BEINGS LEARNED SO DEEPLY, AND SO PAINFULLY, THE EXTENT AND DEPTH OF THEIR IGNORANCE ABOUT NATURE."[4]

WORKING TOGETHER THE HEALTH CARE COMMUNITY, THE ACADEMIC COMMUNITY, AND THE RESEARCH COMMUNITY CAN HAVE THE PRIVILEGE, INDEED THE RESPONSIBILITY, TO DISPEL IGNORANCE AND ITS RESULTS IN SUFFERING FROM DISEASE AND DISABILITY.

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REMARKS*

by

James B. Wyngaarden, M.D.**

Speaking for myself and for my colleagues at the National Institutes of Health (NIH), I wish to express sincere thanks to the Pharmaceutical Manufacturers Association for setting aside time during this annual meeting to call attention to the centennial of our Institution. This thoughtful act mirrors the generous support your members have extended to NIH through the years--and expecially in connection with our centennial events.

We are now in the eighth month of a year-long observance of the 100th anniversary of the establishment of the NIH in a one-room laboratory in the Marine Hospital Service Facility on Staten Island, New York, in August 1887.

In addressing the basic theme "A Century of Science for Health," we have pointed out, in speeches, publications, radio and television announcements and by other means, how much of the significant progress in biomedical science over the past 100 years has been achieved largely through a unique partnership among the Federal Government, academia and industry.

Each member of the partnership has played an important role. The NIH has conducted research in its own laboratories, and has funded a major portion of the basic biomedical research and research training that occurs throughout the Nation. Scientists in the academic world have used funds supplied through the NIH to conduct important basic and applied research. Private industry has conducted its own research studies and has been responsible for the discovery and development of the majority of drugs, medical devices, and health care products in use today.

The industrial, government and academic sectors have become increasingly dependent upon each other in areas related to basic biomedical research. Government and industry depend upon the universities to train the scientists and administrators who will be responsible for the performance of biomedical research. Academia, in turn, benefits from financial support and knowledge provided by government and industry in areas of common interest. Each partner builds on the knowledge acquired and the concepts tested by the others. In this way, our Government, university and industrial laboratories have made the United States a world leader in biomedical research. I must also mention

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*Presented at the Pharmaceutical Manufacturers Association Annual Meeting at the Greenbrier, White Sulphur Springs, West Virginia, May 19, 1987

**Director, National Institutes of Health, Bethesda Maryland

that voluntary health organizations play an important part in this unique partnership. Their support of biomedical research and their public education programs are invaluable in increasing public awareness of the importance of biomedical research and in stimulating new research endeavors.

The NIH came into being at a time when there was general ferment in the sciences. It was a time of solid scientific advances, particularly in biology, chemistry and physics. But almost all of the action was in Europe. Studies of the new discipline, bacteriology, were being carried out in Berlin and Paris by Robert Koch and Louis Pasteur, and their work exerted a pervasive influence on European scientists. When, in the early 1880s, physicians on this side of the Atlantic became deeply worried about the possibility that cholera might be imported into the United States, a young doctor, Dr. Joseph Kinyoun, was sent to study with Pasteur and Koch. Upon his return he set up a bacteriological laboratory known as the Hygienic Laboratory at the Marine Hospital facility on Staten Island, New York. That laboratory ultimately became the National Institutes of Health.

In the course of the intervening century, the NIH has undergone many organizational changes, one amounting almost to a transformation. For the first half of its history the agency was, in essence, a small Federal laboratory carrying out within its own confines important research projects, but its resources were such that at any given time only a limited number of studies could be conducted. It was during the adjustment period following World War II that the near-transformation took place. With demobilization, the Office of Scientific Research and Development (OSRD) went out of business on December 31, 1945, and some 250 biomedical research projects then being funded by the OSRD at universities, hospitals and other research institutions were transferred to the NIH for administration. It is significant that the research projects were not cancelled, and that instead a mechanism was put in place for continuing to award such grants. Peacetime reliance on non-Federal laboratories for the conduct of federally-supported research represented a major change in Federal science policy. This change had the dual effect of confirming NIH's role as the principal biomedical research arm of the government, and establishing extramural grants as the dominant mechanism for the support of such research.

Measured by expenditures, well over four-fifths of NIH research activities take place in nearly 1,300 non-Federal laboratories--most of them within the United States. Thus, almost 90 percent of the NIH's $6.2 billion budget is devoted to extramural awards for research and research training and the necessary administrative costs entailed.

In addition to the grant and contract-supported research, more than 2,500 government scientists participate in research at our main campus in Bethesda, at the National Institute of Environmental Health Sciences at the Research Triangle in North Carolina, at the Rocky Mountain Laboratory in Montana, and in a few small NIH installations elsewhere. These intramural scientists, their collaborating guest workers and the laboratories where they perform their research, constitute what is probably the largest resource of its kind. As large as the intramural program is, however, it is through our extramural programs that we mobilize the energies of some 50,000 American scientists who carry out research under NIH-awarded grants and contracts.

The key mechanism used by the NIH for deployment of the scientific community's creative efforts in biomedical research is the investigator-initiated project grant. Well over one-half or more than 56 percent of our current budget of $6.2 billion is allocated to the support of such project grants for the conduct of research by non-Federal principal investigators. By its very nature, investigator-initiated research taps the expertise and the creativity of the American scientific community.

Over the years the NIH has enjoyed steady and consistent support from the Executive and Legislative Branches of the Federal Government. We believe this favorable treatment results from an appreciation of the overarching importance of research as a necessary step in the development of new means for the prevention or cure of disease and disability. But recently the Administration and the Congress have also become interested in the current economic promise of biotechnology, a direct payoff from the national investment in research.

While many exciting advances are being made in biotechnology today, it is not a new phenomenon. In fact, biotechnology has a long history, certainly as long as that of the NIH. I have mentioned the debt that medicine owes to Pasteur and Koch. We sometimes overlook how industry was a direct object of major portions of Pasteur's work. Perhaps the best way to describe this relationship is to cite the entry on Pasteur in the Encyclopedia Britannica, where his accomplishments are summarized in the following sentence. "Pasteur proved that microorganisms cause fermentation and disease; he originated and was the first to use vaccines for rabies, anthrax, and chicken cholera; he saved the wine, beer and silk industries of France and elsewhere; he performed important pioneer work in stereo-chemistry; (and) he originated pasteurization."

A startlingly similar modern version of this catalog of accomplishments could be written about the results of basic research on molecular biology.

The new linkages that have been established between the NIH and industry have been forged during a period in which industry has supplied an increasing share of the national funding for health research and development. Twenty years ago industry, as a whole, was the source of funding for less than one-fourth of all health research and development; in 1970 it had risen to 28 percent; in 1980 it was 31 percent; and by 1986 industry's share had increased to 39 percent. As a footnote I should mention that in the era of the modern NIH its contribution to national health research and development each year had exceeded the total investment in research by industry until 1983. In 1986, NIH's share was 35 percent compared with industry's 39 percent.

In recent years we have seen the establishment of a number of new ties between industrial organizations and some of the Nation's leading academic institutions. As I have learned more about individual examples of such collaboration, I have been interested to note the many ingenious contractual arrangements that have been devised to serve optimally the purposes of the partners while protecting their individual interests, such as freedom of inquiry, open scientific communications, and proprietary rights. The NIH has an obvious interest in such new partnerships with the academic institutions that for years have been closely linked with us through our extramural programs. We have not assumed any participatory role in the new arrangements and anticipate no change in our existing relationships.

Important links between the NIH and industry were established more than 30 years ago with the establishment of the NIH institutional patent policy in 1953. It was recognized that if valuable fruits of research were to be put into widespread use, substantial outlays would be required for development and marketing. The government is neither a practical nor an appropriate source for most such support, but it was clear that some incentive must be offered to companies to invest in the final stages of development. It was not a simple problem. The new products and processes arising from research conducted with public funds, it was argued, should have been placed in the public domain. To do so, however, would have denied potential developers and marketers the period of exclusivity that induces them to make the necessary additional investment. The NIH recognized that in most cases it would not be reasonable to expect a pharmaceutical company or any other industrial organization to expend funds for development of a product that would not be protected for a time, at least, from competition. Furthermore, NIH cold not be expected to reduce the funds needed for research by expending them in bringing the products of research to the American people. That could have drained the funds required for continuation of research on many fronts.

The NIH patent policy was adopted as a means for breaking the impasse. Each of the institutions receiving grants from NIH was given the opportunity to enter an institutional patent agreement with us. Under the agreement the institutions were encouraged to patent innovations resulting from NIH-supported research and to arrange the licensing for development and marketing of such innovations. The NIH patent agreements provide that the institutions themselves receive a major share of the royalties from such licenses but that they must reinvest such proceeds in further biomedical research. The investors also were permitted to share in the proceeds. The NIH did not participate in the income from such extramural licensing agreements.

Most of the features of the long-standing NIH patent policy were embodied without change in the Stevenson-Wydler Technical Innovation Act of 1980. Amendments to the Act, approved in 1986, established procedures for dealing with the royalties on inventions in Federal laboratories.

In other, more direct ways, NIH's relationships with industry have become more extensive. An example is liberalization of our policy in the area of grants. Until the early 1960s the NIH had accepted grant applications from institutions regardless of their "for-profit" or "non-profit" status. In the mid-60s congressional concerns prompted a change in that policy so that only not-for-profit organizations were considered eligible for grants. This restrictive policy was abandoned in December 1982 so that grant applications may be received, reviewed and, if of sufficient merit, awarded to industrial organizations as well as to the traditional grantees. Thus, NIH-funded programs can have access to the creative abilities of outstanding scientists employed by industry, and conversely, these scientists have access to sources of funding for research projects that might not be appropriate objects of company support. Such grants do not now constitute more than a small fraction of our total portfolio and probably will not increase markedly in the foreseeable future.

A new type of grant, however, was created by the Congress in 1982 through legislation requiring that a specified percentage of the annual appropriations of Federal research agencies be awarded for research by small business

organizations. The NIH Small Business Innovation Research Program funded 445 grants in 1986 for a total of $44.5 million. Such awards are made on the basis of the merit evaluations by initial review groups operating in much the same manner that the traditional research study sections assess proposals.

At a number of the centennial observances in which I have participated, I have been asked to make predictions about NIH's second century. To forecast developments in an area as dynamic as the biosciences is hazardous--some might say foolhardy. But in considering what the second century will bring in all areas of NIH-conducted and supported biomedical research, it seems certain that molecular biology and its related disciplines will play a major role.

Historians of science will probably say that the most significant contribution of the NIH thus far has been the support of pioneering work in molecular biology that began to flower in the 1950s and continues unabated. This research has led to a virtual explosion extending across all biological sciences. It is the foundation for the recombinant DNA technique whose possibilities are only beginning to be realized. As you know, an entirely new biotechnology industry is based on the recombinant DNA discoveries.

As science has grown more sophisticated in recent decades and has begun to focus on problems of increasing complexity, collaboration has grown between scientists from various disciplines. This movement toward multidisciplinary research has fostered communications between scientific disciplines and has provided promising approaches to research problems that earlier had remained intractable.

Technological advances in areas such as x-ray crystallography and magnetic resonance imaging provide new opportunities to investigate the structural properties of physiologically active molecules. One of the most rapidly evolving research tools now being used by molecular biologists is magnetic resonance imaging spectroscopy. Using this technique it is possible to determine the chemical composition of biologically important molecules, the length and nature of the bonds holding the atoms of the molecules together, and the three-dimensional arrangement of these molecules. A significant advantage of this technique is that studies can now be performed on molecules in their typical physiologically active state, that is, either within the living organism or in an aqueous rather than in an unnatural solid state.

The promise of the various new approaches to drug development has led NIH toward a special initiative to develop targeted antiviral compounds, particularly focused on AIDS. It is expected that these efforts will bring together multidisciplinary teams of scientists in such areas as x-ray crystallography, magnetic resonance imaging, molecular modeling, drug design and synthesis and virology.

In the years past a number of genetic diseases--particularly inborn errors of metabolism--yielded to scientists using biochemical methods to identify the defective gene product, such as a faulty protein. They then worked back to the molecular basis of the disorder, such as the replacement of one amino acid by another. The DNA error that produced the amino acid replacement could then be inferred.

Now, thanks to the science of molecular genetics it is possible to identify the gene at fault without identifying the primary gene product or the basic biochemical mechanism of the disease. Chromosomal localization of the responsible genes has been accomplished for Huntington's disease, cystic fibrosis, Duchenne muscular dystrophy, retinoblastoma, and Alzheimer's disease. These gene markers are already proving useful in the clinic for genetic counseling.

Molecular biology has progressed to the point where it is now possible to characterize the human genome by obtaining complete nucleotide sequences of its three billion components. This new knowledge would greatly enhance our understanding of the molecular mechanisms that control gene expression and the molecular bases for inherited disease; we would gain substantial new information on neoplastic and malignant disorders as well as on autoimmune and immunodeficiency diseases. The information to be gained from characterizing the human genome would create an extensive new science base of special importance to studies of toxicology and the effects of environmental contaminants, and the potential for effective gene therapy would be enhanced.

It is clear that the technology exists for completing a major portion, if not all of the task. There is general confidence that the necessary improvements in methodology will be developed to deal with certain problem areas and thus eventually to make possible the total characterization. It is early to embark on a massive program because automated instruments now on the horizon hold out the prospect of reducing the ultimate cost by an order of magnitude or more.

The figure of $3 billion has been given as a cost estimate of a full program, based on the calculation that there are about three billion nucleotides in the human genome and that it will cost about $1 per nucleotide. Within a few years, however, this could be reduced to about $.10 per nucleotide, dropping the total cost of the program to $300 million.

I have mentioned a few of the promises held by the years ahead as the National Institutes of Health enters its "second century of science for health," an era in which the productive collaboration among academia, industry and the Government will grow even more effective than before.

The U.S. biomedical research and development enterprise is currently looked to by the world's scientists for leadership. If America's young people show heightened interest in research careers, and if Government, academia and industry can depend upon predictable levels of support for biomedical research, our country can maintain its leadership. More is at stake than position. Such efforts can continue to accelerate the biomedical revolution that promises rapid progress against the old enemies of disease through knowledge about new means for prevention, effective treatment and cure.

NIH SUPPORT OF MEDICAL GENETICS*

by

James B. Wyngaarden, M.D.**

I am pleased to have this opportunity to participate in the FAES Colloquium on Financing Medical Genetics in the United States. In my presentation, I will discuss the support of medical genetics by the National Institutes of Health (NIH), describe several of our current programs, and sketch briefly some of our plans for the future.

A major goal of the research conducted and supported by the National Institutes of Health is an understanding of the genetics of normal human development and function, as well as of what goes awry in human disease. In 1986 alone, NIH provided about $300 million for studies of complex genomes, both human and non-human. Of this, about $90 million was devoted to research directly related to human genetics.

Over the years, NIH funding has aided the development of recombinant DNA technology, the use of restriction fragment length polymorphisms to detect markers for disease genes, the development of techniques for walking and jumping from a marker to a gene, and the creation of important new methods of separating large fragments of DNA.

These technical achievements have led to greater understanding of specific genetic diseases. For example, NIH grantees have recently been involved in identifying the genes for Duchenne muscular dystrophy and retinoblastoma. Other grantees have located genetic markers for Huntington's disease, cystic fibrosis, Alzheimer's disease, and manic-depressive illness. The Huntington's disease marker was found in a relatively short period of time, in part due to NIH's creation of a special organizational entity to study the disease. This entity, the "Center Without Walls," links scientists at different institutions in a multidisciplinary effort to understand the basic mechanisms of Huntington's disease and to find ways to diagnose and prevent it. The work on manic-depressive illness has provided the first firm evidence of a connection between a gene and a mental illness.

Ongoing basic research using a variety of model systems will further enhance our understanding of fundamental genetic processes--and ultimately, our ability to conquer genetic diseases.

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*Opening remarks before the Foundation for Advanced Education in the Sciences Colloquium on Financing Medical Genetics in the United States, Bethesda, Maryland, May 20, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Genetic Screening

NIH has supported the development and evaluation of a variety of genetic screening methods. One that is currently under study is chorionic villus sampling, which is undergoing a clinical trial at seven research centers. The trial will examine the accuracy and safety of the procedure, and will compare it with the accuracy and safety of amniocentesis.

Mechanisms of Support

NIH funds genetics research through a variety of support mechanisms, chief among them the traditional investigator-initiated research grant. Groups of scientists working together on a common problem may receive program project grants. Large, multidisciplinary efforts--often those that bridge the gap between research and clinical applications--are supported via research center grants. Research resources and clinical trials are usually funded through contracts or cooperative agreements.

NIH also underwrites the research training of many scientists who are studying aspects of genetics. A special initiative to train more physician-scientists should have an impact on clinical genetics research and practice.

General Clinical Research Centers

A special type of research center is sponsored by the NIH Division of Research Resources. General Clinical Research Centers, or GCRC's, conduct clinical research on the causes, prevention, control, and cure of human diseases, including genetic disorders. At the GCRC at Emory University, for example, scientists are studying genetic mechanisms responsible for severe insulin resistance using the autosomal recessive trait known as Leprechaunism as a model. Other Emory researchers have localized the gene for Emery-Dreifuss muscular dystrophy to the distal portion of the long arm of the X chromosome. Grantees at the Rockefeller University GCRC have found that a common polymorphism of apolipoprotein E profoundly influences dietary fat clearance. And at the GCRC at Yale University, a study of Tourette syndrome is providing new information on familial patterns of transmission as well as on symptom variations.

Cell Repository

Another way in which NIH makes significant contributions to genetics research is through its support of resources like the Human Genetic Mutant Cell Repository. This repository was established by the National Institute of General Medical Sciences in 1972 at the Coriell Institute for Medical Research in Camden, New Jersey. Under the current 5-year contract, NIH will spend $4 million on this effort.

The repository establishes and stores cell lines from patients with genetic disorders and, if warranted, from members of their families. All cell lines are characterized cytologically and/or biochemically, and are distributed to interested scientists for a modest fee.

The collection includes fibroblast and lymphoblast lines from individuals with a range of inherited metabolic diseases as well as from individuals with disorders characterized by chromosomal abnormalities. The repository also contains a number of special collections of cell lines representing diseases for which the cellular defect cannot, as yet, be demonstrated in culture. Some of the cell lines come from members of large families, and are valuable for detecting markers for disease genes--and eventually for identifying the genes themselves.

GenBank®

Several years ago, it became clear that an organized effort was needed to store, catalog, and distribute the nucleotide sequence data that were--and still are--being generated so rapidly. In 1979, Dr. Walter Goad of the Los Alamos National Laboratory began a DNA sequence data base as a pilot project. During that year, the National Science Foundation sponsored a workshop at which participants agreed that a centralized data bank was essential. In early 1980, Dr. Greg Hamm of the European Molecular Biology Laboratory in Heidelberg, West Germany, began a European data base. That July, the National Institute of General Medical Sciences held a workshop that led to the creation of the Genetic Sequence Data Bank, commonly known as GenBank®.

GenBank® is an interagency effort, with staff of the National Institute of General Medical Sciences serving as the project officers. Contributors include four NIH institutes, the National Science Foundation, and the Departments of Energy and Agriculture. The GenBank® budget was $504,000 in fiscal year 1986. Over the 5 years of the contract, the Federal Government will spend about $3.5 million on GenBank®.

GenBank® currently contains about 11,000 sequences, representing 11 million base pairs. It now takes 5 months for a newly published sequence to be entered in GenBank®, down from 12 or more months a year ago.

Since GenBank® was established in 1982, the number of sequences appearing in the scientific literature has increased tenfold. We expect an even more dramatic rise in the future, due to advances in DNA sequencing technologies and increasing interest in sequencing the human genome. The issue of how to manage the data base most efficiently and keep pace with the explosion of new sequence data is now being discussed. Part of the answer is to continue the extensive, successful collaboration between GenBank® and its European counterpart.

BIONET

Complementary to GenBank® is BIONET, a resource that provides computational assistance in data analysis and problem-solving to molecular biologists and researchers in related fields. BIONET also serves as a focus for the development and sharing of new computer software, as well as for scientific collaboration in this area.

BIONET was established in 1984 under a cooperative agreement between the Division of Research Resources and the Intelligenetics Division of Intellicorp, a company located in Palo Alto, California. The cost of the resource is about $3.7 million over a 5-year period.

BIONET consists of a data base library that contains existing nucleic acid and protein sequence data bases, including the GenBank® and European Molecular Biology Laboratory data bases; the National Biomedical Research Foundation library of protein sequences; VectorBank, which has maps of often-used cloning vectors assembled by Intelligenetics; and a restriction enzyme data base from Cold Spring Harbor Laboratories.

Other Resources

In late 1985, NIH established a repository of human DNA probes, operated by a 5-year, $1.5 million contract to the American Type Culture Collection in Rockville, Maryland. The repository already contains some chromosome-specific DNA libraries developed by the Department of Energy, and will acquire additional ones. It is also collecting cloned human genes and anonymous human DNA probes.

While NIH is counting on the promise of molecular genetics, it is by no means neglecting the more classical approaches. For example, we support annual workshops that encourage collaborations to refine and develop methodologies for the analysis of human pedigree data. This international effort involves theoreticians, clinicians, genetic epidemiologists, and computer experts. Participants address complex issues such as the relative contribution of genetic and environmental factors to human traits, the identification of gene complexes that affect the expression of disease, and the development of an accurate linkage map. The contributions of these workshops to the identification and mapping of the gene sequences that affect polygenic diseases such as diabetes, cancer, and heart disease have been especially useful.

New Method of DNA Analysis

I would like to tell you about an exciting new development with immediate and long-range implications for medical genetics. This work takes the fruits of basic research--the isolation of disease genes and an understanding of their structure and function--and combines them with new techniques to speed the detection of genetic disorders.

Building on techniques developed by NIH scientists and grantees, in late 1985 researchers at the Cetus Corporation in Emeryville, California, developed a new method of DNA analysis that is faster, easier, and more reliable than existing techniques. The first step in the process is called the polymerase chain reaction. It allows the exponential amplification of a specific DNA sequence by repeated rounds of DNA replication. One microgram of DNA can easily provide enough material to perform a diagnostic test, making it unnecessary to culture cells from amniocenteses or blood samples. Once the amplified sequence is in hand, a second procedure, called oligomer restriction, is used to detect abnormal genetic material more rapidly and accurately. Used together, these techniques can cut the length of time a diagnostic test takes from several weeks to one day.

NIH helped support the successful use of these procedures to determine if expectant parents or their fetuses carried a gene for sickle cell anemia. In the future, these techniques are likely to have broad applications in basic research as well as in clinical settings.

Director's Advisory Committee Meeting

I have described how NIH has been actively involved in human genetics for some time. Obviously, we are committed to continuing and expanding such activities. To discuss what NIH's role should be in future efforts to map and sequence the human genome, I asked the advisory committee to the NIH Director to focus on this issue at its October 1986 meeting. The group reached a consensus on the importance of understanding the genomes of a number of organisms, not just that of humans. Among the other major conclusions were the following:

- Proceed with the construction of physical and genetic maps with all due speed;
- Postpone exhaustive sequencing efforts until the technology matures;
- Improve technologies for cloning large DNA fragments and for sorting, mapping, and sequencing genes more rapidly and efficiently, with a lower error rate;
- Coordinate and improve the handling of information generated by mapping and sequencing to assure access by scientists throughout the world; and
- Promote interagency and international cooperation.

Recent Developments

Following the October meeting, I established an NIH working group to implement the advisors' recommendations. The goal of improving data base management was addressed at a February 1987 meeting in Heidelberg, at which representatives of GenBank® and the European Molecular Biology Laboratory discussed ways to assure prompt, easy, and complete access to the rapidly

accumulating mapping and sequencing information. The Japanese have also expressed an interest in becoming involved in this international biological data base effort.

NIH will soon issue two program announcements encouraging independent investigators to submit research grant applications in a number of areas related to the characterization of the human genome.

Finally, a subcommittee of the White House Domestic Policy Council has been established to assure that Executive Branch agencies share information and coordinate their activities on the human genome. I am chairing this group. NIH is committed to such cooperation, not only at the national level but also with private, academic, industrial, and international groups as we all pursue the exciting scientific opportunities of basic and clinical genetics.

Thank you for the opportunity to take part in this program. I would be pleased to respond to your questions.

REMARKS*

BY

J. EDWARD RALL, M.D., Ph.D.**

SINCE THE CENNTENNIAL OBSERVANCE BEGAN LAST OCTOBER, I HAVE PARTICIPATED AS A SPEAKER AT QUITE A FEW EVENTS WHERE THE NIH CENTURY WAS BEING HONORED. IN EACH OF THESE TALKS I HAVE INCLUDED AT LEAST A BIT OF THE HISTORY OF THE DEVELOPMENT OF THIS EXTRAORDINARY INSTITUTION, AND THIS HAS ENTAILED A SEARCH OF MATERIALS SUCH AS: BESS FURMAN'S "HISTORY OF THE U.S. PUBLIC HEALTH SERVICE"; DR. STETTEN'S EXCELLENT COLLECTION OF HISTORICAL ARTICLES ON THE INTRAMURAL RESEARCH PROGRAM; VICTORIA HARDEN'S BOOK ON "INVENTING THE NIH"; AND OTHERS. BUT EVEN WITH THESE VALUABLE SOURCES THERE REMAIN GAPS IN THE STORY. IT IS IMPRESSIVE HOW IN THE RELATIVELY SHORT SPAN OF 100 YEARS THE RECORDS AND MEMORY OF IMPORTANT EVENTS CAN FADE OR UNDERGO DESTRUCTIVE MUTATIONS. THUS, I THINK IT IS ESPECIALLY APPROPRIATE THAT AS ONE OF OUR CENTENNIAL ACTIVITIES WE ARE ESTABLISHING AN ENTITY WHOSE PURPOSES WILL INCLUDE THE CONSERVATION OF OBJECTS, DEVICES AND INFORMATION ASSOCIATED WITH THE PAST AND THE PRESENT OF BIOMEDICAL RESEARCH. IN DR. STETTEN'S WORDS, "THIS MUSEUM REPRESENTS OUR HERITAGE AT NIH. LIKE OUR PUBLICATIONS, IT IS A PART OF THE RECORD OF ACCOMPLISHMENT, BUT THE OBJECTS ARE SOMEWHAT MORE ENDURING."

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*PRESENTED FOR THE DIRECTOR, NIH, AT THE DEDICATION OF THE MUSEUM FOR BIOMEDICAL RESEARCH, ACRF LOBBY, WARREN GRANT MAGNUSON CLINICAL CENTER, MAY 21, 1987.

**DEPUTY DIRECTOR, FOR INTRAMURAL RESEARCH NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

INVESTIGATORS.

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REMARKS*

BY

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REMARKS*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM GRATEFUL, INDEED, FOR THE HONOR YOU HAVE GIVEN ME, AND I SHALL CHERISH MY STATUS AS AN HONORARY ALUMNUS OF TEL AVIV UNIVERSITY. I ALSO CONSIDER IT A SPECIAL PRIVILEGE TO BE A MEMBER OF THIS "CLASS" OF AWARDEES--DISTINGUISHED [illegible] FROM MANY DIFFERENT PARTS OF THE WORLD, AND I [illegible] HAVE BEEN GIVEN THIS OPPORTUNITY TO SPEAK BRIEF[illegible] BEHALF.

THE RANGE OF ACCOMPLISHMENTS REPRESENTED BY THE PERSONS RECEIVING HONORARY DEGREES AND FELLOWSHIPS IS IMPRESSIVE. THE PERSONS BEING HONORED HAVE ACHIEVED DISTINCTION IN SUCH DIFFERENT FIELDS AS PHYSICS, HISTORY, MUSIC, VISUAL COMMUNICATIONS AND DEVOTED LEADERSHIP IN THE SUPPORT OF HIGHER EDUCATION. THE SCOPE OF INTERESTS THEY REPRESENT IS SYMBOLIC OF THE INTELLECTUAL RANGE OF A GREAT INSTITUTION. IN A SHORT PERIOD, AS TIME IS MEASURED IN THE LIFE OF INSTITUTIONS OF HIGHER LEARNING, TEL AVIV UNIVERSITY HAS ESTABLISHED AN EDUCATIONAL PROGRAM OF DEPTH AND DIVERSITY. SUCH UNIVERSITIES RENDER NECESSARY AND EXTREMELY VALUABLE SERVICE TO SOCIETY THROUGH THEIR ENHANCEMENT OF THE INTELLECTUAL, SPIRITUAL, PHYSICAL AND

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*PRESENTED ON BEHALF OF ALL THE HONORARY DEGREE RECIPIENTS AT THE UNIVERSITY OF TEL AVIV IN ISRAEL, MAY 24, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

MATERIAL RESOURCES OF PEOPLES AND NATIONS. THEIR PROFESSIONAL SCHOOLS ARE INDISPENSABLE SERVANTS OF MODERN SOCIETY. RECOGNIZING THAT THE SUPPORT FOR HIGHER EDUCATION WOULD HAVE TO COME FROM A VARIETY OF SOURCES, INCLUDING THE GOVERNMENT, AND IN DEFENDING THE USE OF PUBLIC FUNDS FOR THIS PURPOSE, THOMAS JEFFERSON ONCE DESCRIBED THE UNIVERSITY AS THE "MOST LEGITIMATE ENGINE" OF GOVERNMENT.

AMONG THE NATIONS, ISRAEL IS WELL-KNOWN FOR THE RESPECT SHOWN BY ITS PEOPLE FOR THE NECESSITY OF EDUCATION AND FOR THE VALUE OF HIGHER EDUCATION. THE CONSTANCY OF COMMITMENT TO EDUCATIONAL EXCELLENCE BY ITS MANY FRIENDS, EVEN IN DIFFICULT TIMES, HAS SERVED WELL THE CAUSE OF HIGHER EDUCATION IN ISRAEL.

FARSIGHTEDNESS HAS PROMPTED INDIVIDUALS, INSTITUTIONS AND GOVERNMENTS TO INVEST SUBSTANTIALLY IN PROVIDING YOUNG PEOPLE THE EDUCATIONAL OPPORTUNITIES AVAILABLE IN UNIVERSITIES OF THIS KIND. THIS ESSENTIAL INVESTMENT IS MADE BECAUSE OF THE CONVICTION THAT IT WILL GENERATE RICH RETURNS FOR SOCIETY, ALTHOUGH NO ONE KNOWS EXACTLY HOW, WHERE, OR WHEN. IN MUCH THE SAME WAY THE SUPPORT OF BASIC RESEARCH IS AN ACT OF FAITH. BUT IT IS AN INVESTMENT WHOSE UNPREDICTABLE, BUT MAGNIFICENT RESULTS HAVE BEEN REALIZED SUFFICIENTLY OFTEN TO JUSTIFY PRAGMATICALLY THE PURSUIT OF FUNDAMENTAL KNOWLEDGE.

In the area of health research the incentive--the social payoff--is compelling. One of the richest benefits from higher education in our time derives from its association with health-related research and the accomplishments that have been made through biomedical research. Its significance is essentially universal, for as Disraeli said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."[1]

Israeli contributions to basic knowledge in the biological sciences are well known, certainly in the United States. Our countries have collaborated in many areas of sciences, and especially in biomedical investigations. An outstanding example of such collaboration takes place in the intramural laboratories of the National Institutes of Health. To describe this activity, permit me to say a bit about the institution.

Almost 90 percent of our budget is allocated to the support of research through contracts and grants at academic centers, hospitals and independent laboratories throughout the United States, and in many other countries, including Israel. But an extremely important part of our research activities takes place in our own laboratories. This year the budget for intramural research will total almost $660 million. Almost 3,000 doctoral-level government scientists, and as many as 3,500 trained support staff, are engaged in our in-house

RESEARCH PROGRAM. THE INTRAMURAL RESEARCH ACTIVITIES ARE CARRIED OUT IN A GREAT NUMBER OF DIFFERENT UNITS, SOME WITH SPECIFIC GOALS, AND OTHERS ALLOWED TOTAL FREEDOM TO PURSUE SCIENTIFIC CLUES WHEREVER THEY MAY LEAD. SOME OF OUR LABORATORIES ARE CLINICALLY ORIENTED, AND OTHERS HAVE INTERESTS IN BASIC BIOLOGY AS, FOR EXAMPLE, STUDIES IN MOLECULAR BIOLOGY. THROUGH THE YEARS ISRAELIS HAVE CONSTITUTED A SIZEABLE PART OF THIS SCIENTIFIC COMMUNITY, AS VISITING COWORKERS.

TALENTED SCIENTISTS FROM THROUGHOUT THE WORLD COME TO BETHESDA TO SHARE IN THE RESOURCES OF OUR LABORATORIES, AND TO SHARE THEIR KNOWLEDGE AND EXPERTISE WITH THEIR FELLOW SCIENTISTS. THROUGH OUR VISITING SCIENTIST PROGRAMS, DISTINGUISHED INVESTIGATORS AT ALL LEVELS OF THEIR CAREERS ARE INVITED TO CONDUCT RESEARCH IN THEIR OWN AREAS OF INTEREST AND, IF DESIRED, TO RECEIVE FURTHER TRAINING. STIPENDS ARE PROVIDED AND EACH PARTICIPANT IN THE VISITING PROGRAM WORKS CLOSELY WITH A SENIOR NIH INVESTIGATOR WHO SERVES AS HOST OR SPONSOR DURING A VISITOR'S PERIOD OF AWARD OR APPOINTMENT. CURRENTLY, OVER 1,100 SCIENTISTS FROM MORE THAN 70 COUNTRIES ARE PARTICIPATING IN OUR VISITORS' PROGRAMS, INCLUDING MORE THAN 50 FROM ISRAEL. IN ADDITION, ABOUT 400 GUEST WORKERS ALSO PARTICIPATE IN RESEARCH AT THE NIH. THESE SCIENTISTS DO NOT RECEIVE STIPENDS BUT ARE PROVIDED LABORATORY SPACE AND RESEARCH SUPPORT.

IN 1969 THE FOGARTY INTERNATIONAL CENTER OF THE NATIONAL INSTITUTES OF HEALTH ESTABLISHED THE SCHOLARS-IN-RESIDENCE

PROGRAM, TO WHICH A FEW WELL ESTABLISHED SCIENTISTS AND SCHOLARS INTERESTED IN ISSUES OF INTERNATIONAL HEALTH ARE ELECTED. THE SCHOLARS ARE INVITED TO SPEND UP TO 12 MONTHS AT THE NIH TO EXCHANGE INFORMATION AND IDEAS, AND PARTICIPATE IN RESEARCH IN AN ENVIRONMENT CONDUCIVE TO INNOVATIVE ADVANCED STUDIES. NOMINATIONS FOR THE SCHOLARS-IN-RESIDENCE ARE REVIEWED BY A PANEL OF NIH INTRAMURAL SCIENTISTS AND APPROVED BY THE FOGARTY ADVISORY BOARD. SINCE THE BEGINNING OF THE PROGRAM 149 SCHOLARS-IN-RESIDENCE HAVE BEEN SELECTED AND HAVE COME TO NIH. OF THIS NUMBER 22 ARE FROM ISRAEL. IN FACT, THE FIRST FOGARTY SCHOLAR-IN-RESIDENCE WAS URIEL LITTAUER FROM ISRAEL. TWO SCIENTISTS FROM TEL AVIV UNIVERSITY WERE FOGARTY SCHOLARS-IN-RESIDENCE, DR. BRACHA RAMOT AND DR. MORDECHAI SOKOLOVSKY.

A MOMENT AGO I MENTIONED NIH'S WIDESPREAD INVOLVEMENT IN THE SUPPORT OF RESEARCH AT ACADEMIC INSTITUTIONS. THIS HAS BEEN A DOMINANT FEATURE OF OUR PROGRAMS SINCE THE MID-1940S. WE FEEL VERY CLOSE TO ACADEMIC INSTITUTIONS AND IN MANY WAYS--BOTH ORGANIZATIONALLY AND OPERATIONALLY--THE NIH RESEMBLES A UNIVERSITY. OUR RESEARCH SUPPORT PROGRAMS WERE ESTABLISHED AND CONTINUE TO FLOURISH ON A PHILOSOPHICAL FOUNDATION WHOSE ORIENTATION TOWARD RESEARCH IS ESSENTIALLY THE SAME AS THAT ON WHICH GREAT UNIVERSITIES ARE BUILT.

WHEN THE END OF WORLD WAR II COULD BE FORESEEN, PRESIDENT ROOSEVELT ASKED THE EMINENT SCIENTIST-EDUCATOR VANNEVAR BUSH

TO CHART A COURSE FOR POST-WAR SCIENCE. IN HIS REPORT CALLED "SCIENCE--THE ENDLESS FRONTIER," BUSH STRONGLY RECOMMENDED THAT THE GOVERNMENT CONTINUE TO INVEST IN RESEARCH, PARTICULARLY IN THE HEALTH FIELD. HE POINTED OUT THE CRUCIAL IMPORTANCE OF ACADEMIC INSTITUTIONS IN CARRYING OUT SUCH A GOVERNMENT ACTIVITY. THE DOCUMENT WAS A LANDMARK IN GOVERNMENT SCIENCE POLICY AND MANY OF ITS RECOMMENDATIONS CONTINUE TO GUIDE OUR FEDERAL RESEARCH AGENCIES, INCLUDING THE NIH.

PERMIT ME TO QUOTE FROM THE REPORT. BUSH CHARACTERIZED PUBLICLY AND PRIVATELY SUPPORTED COLLEGES, UNIVERSITIES, AND RESEARCH INSTITUTES AS "....WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING." HE SAID THAT, "AS LONG AS THEY ARE VIGOROUS AND HEALTHY AND THEIR SCIENTISTS ARE FREE TO PURSUE THE TRUTH WHEREVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE. FOR SCIENTIFIC PROGRESS," HE SAID, "....RESULTS FROM THE FREE PLAY OF FREE INTELLECTS WORKING ON SUBJECTS OF THEIR OWN CHOICE IN THE MANNER DICTATED BY THEIR CURIOSITY FOR EXPLANATION OF THE UNKNOWN."[2]

WE HAVE SEEN THE FRUITS OF THAT PRESCRIPTION FOR SCIENTIFIC PROGRESS. THE SURGE OF DISCOVERY THAT HAS TAKEN PLACE IN THE BIOSCIENCES IN LESS THAN A GENERATION IS WITHOUT PRECEDENT.... AND IT IS GATHERING STRENGTH. NOT LONG AGO, SCIENCE MAGAZINE PUBLISHED A COLLECTION OF RESEARCH PAPERS UNDER THE GENERAL HEADING OF THE "REVOLUTION IN BIOLOGY." THE LEAD ARTICLE, TITLED "BIOLOGICAL FRONTIERS," WAS WRITTEN BY BIOPHYSICIST

FREDERICK R. BLATTNER. HE WROTE, "PHILOSOPHERS AND HISTORIANS OF SCIENCE WILL PROBABLY REGARD THE CURRENT PERIOD AS A TIME OF EXPLOSIVE ADVANCE AND REFINEMENT ON INFORMATION RATHER THAN A TRUE REVOLUTION. IT HAS NOT BEEN NECESSARY, HOWEVER, AS WAS THE CASE WITH THE QUANTUM THEORY OR RELATIVITY, TO OVERTURN MAJOR PARADIGMS OF ACCEPTED THOUGHT. RATHER," HE SAID, "AN ENORMOUS INCREASE IN THE POWER OF EXPERIMENTAL TECHNIQUES IS NOW PRODUCING ANSWERS TO COMPLEX, LONG-STANDING BIOLOGICAL QUESTIONS."[3]

WHETHER TERMED AS EXPLOSION OR A REVOLUTION, IT IS AN EXCITING TIME INDEED, AND ALL WHO HAVE A ROLE IN THE BIOLOGICAL SCIENCES TODAY CAN FEEL FORTUNATE TO BE AN ACTIVE PARTICIPANT IN A SCIENCE WHERE ADVANCES ARE BEING MADE AT THE LIMITS OF KNOWLEDGE.

MEDICAL SCIENCES HAVE INDEED MADE GREAT STRIDES IN THE PAST 40 YEARS. FIELDS SUCH AS GENETICS, VIROLOGY, MOLECULAR BIOLOGY, BIOCHEMISTRY, IMMUNOLOGY, AND THE BIOSCIENCES HAVE ATTRACTED THE BRIGHTEST AND MOST PRODUCTIVE INVESTIGATORS OF OUR ERA. DISCOVERIES HAVE COME SO FAST THAT IT IS ALMOST IMPOSSIBLE TO KEEP UP WITH THESE HIGHLY SPECIALIZED FIELDS. NEWLY DEVELOPED INSTRUMENTATION--TAKING US FROM VACUUM TUBES TO TRANSISTORS, TO COMPUTER CHIPS; FROM X-RAYS TO CAT SCANS, TO POSITRON EMISSION TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING--HAS PERMITTED AMAZING LEAPS IN OUR FUNDAMENTAL UNDERSTANDING OF HUMAN BIOLOGY. IN PARTICULAR, SCIENTIFIC

ATTENTION TODAY IS FOCUSED ON THE STRUCTURAL BIOLOGY OF ORGANISMS AT THE CELLULAR AND MOLECULAR LEVEL AND ON THE MECHANISMS BY WHICH THEY FUNCTION PROPERLY OR FAIL.

THESE ARE MORE THAN SPECULATIVE OR THEORETICAL EXCURSIONS. AT THIS TIME, FOR EXAMPLE, THE NIH IS USING THE TECHNIQUES OF A RELATIVELY NEW FIELD, STRUCTURAL BIOLOGY, IN A SPECIAL EFFORT TO DEVELOP ANTIVIRAL DRUGS, INCLUDING FIRST OF ALL, ONE THAT WILL TARGET THE AIDS MACROMOLECULE. FUNDAMENTAL RESEARCH IN STRUCTURAL BIOLOGY IS CENTRAL TO THE DEVELOPMENT OF THE FAMILY OF ANTIVIRAL DRUGS.

WHENEVER A SPECIFIC NUCLEIC ACID CAN BE IDENTIFIED AS ESSENTIAL TO THE REPLICATION OF THE AIDS VIRUS, IT IS POSSIBLE TO DESIGN AN ANTIVIRAL DRUG THAT CAN INTERFERE WITH ITS REPLICATION. IT IS HOPED THAT OUR SPECIAL RESEARCH PROGRAM WILL LEAD TO DEVELOPMENT OF SEVERAL PRINCIPLES AND GUIDELINES FOR DESIGNING AND REGULATING ANTIVIRALS.

TODAY, SCIENTISTS AT NIH AND ELSEWHERE ARE GIVING SERIOUS CONSIDERATION TO THE WISDOM OF PROPOSALS TO ATTEMPT TO CHARACTERIZE THE ENTIRE THREE BILLION NUCLEOTIDE HUMAN GENOME. A DECADE AGO THIS PROJECT WOULD HAVE SOUNDED LIKE SCIENCE FICTION, BUT THE FACT IS THAT THE TECHNOLOGY FOR ACCOMPLISHING IT EXISTS TODAY. WHETHER SUCH AN ENDEAVOR IS PRACTICAL, CONSIDERING THE RESOURCES AVAILABLE, IS THE QUESTION BEING DEBATED.

THE HUMAN GENOME PROJECT IS POSSIBLE BECAUSE MOLECULAR BIOLOGY HAS TAUGHT US MUCH ABOUT THE MECHANISMS OF GENE EXPRESSION AND THE MOLECULAR BASES OF INHERITED DISEASES (MALIGNANT NEOPLASMS, IMMUNE DEFICIENCIES, AUTOIMMUNE DISEASES). THE PROJECT COULD COST $3 BILLION AND TAKE TEN YEARS, BUT COULD HAVE VERY POSITIVE OUTCOMES. CONSIDER, FOR EXAMPLE, THAT 4,000 HUMAN DISEASES HAVE A GENETIC BASIS, INCLUDING CYSTIC FIBROSIS, DUCHENNE-TYPE MUSCULAR DYSTROPHY, HUNTINGTON'S DISEASE, AND ALZHEIMER'S DISEASE. SUCH A PROJECT COULD RESULT IN DISCOVERY AS TO WHY SOME PERSONS GET DISEASES SUCH AS CANCER, HEART DISEASE, MENTAL ILLNESS, AND OTHERS DO NOT. AND SUCH A PROJECT WOULD PROVIDE AN EXPONENTIAL INCREASE IN KNOWLEDGE OF HUMAN BIOLOGY.

THERE IS GENERAL CONFIDENCE THAT NECESSARY IMPROVEMENTS IN METHODOLOGY WILL BE DEVELOPED TO DEAL WITH CERTAIN PROBLEM AREAS AND THUS EVENTUALLY TO MAKE POSSIBLE THE TOTAL CHARACTERIZATION.

ONE OF THE MOST PRESSING PROBLEMS IS TO DEVISE MEANS FOR DEALING WITH THE VAST AMOUNT OF DATA THAT WILL BE GENERATED IN THE GENOME PROJECT. DATABASES THAT HAVE BEEN ESTABLISHED TO HANDLE SUCH INFORMATION ARE CURRENTLY SWAMPED. IT HAS BEEN ESTIMATED THAT THE PROJECT WILL CALL FOR THE HANDLING AND STORAGE OF AT LEAST 1000 TIMES AS MUCH INFORMATION AS IS CURRENTLY BEING PROCESSED.

IN THIS PROJECT, AS WELL AS MANY OTHERS IN BASIC SCIENCE TODAY, INTERNATIONAL COOPERATION IS AN IMPORTANT ELEMENT; IN FACT, IN THIS PARTICULAR PROJECT IT IS ESSENTIAL IF CHAOS IS TO BE AVOIDED IN DEALING WITH THE INFORMATION GENERATED FROM MAPPING ANY SEQUENCING ACTIVITIES TAKING PLACE IN MANY DIFFERENT PARTS OF THE WORLD. SUCH SEEMINGLY SMALL MATTERS AS ADHERENCE TO UNIFORMITY OF TERMINOLOGY CAN BECOME A FINAL DETERMINANT OF THE SUCCESS OF THE GENOME EFFORT.

IN THE ROSTER OF REASONS FOR CONDUCTING BIOMEDICAL RESEARCH, THE IMPROVEMENT OF HUMAN HEALTH CONSTITUTES A COMPLETE JUSTIFICATION. SUCH RESEARCH CAN ALSO BE JUSTIFIED AS A MEANS FOR MEETING THE INSATIABLE HUMAN NEED TO KNOW. IN RECENT YEARS, A THIRD REASON HAS COME INTO PROMINENCE--BIOMEDICAL RESEARCH AS A FOUNDATION FOR BIOTECHNOLOGY.

WHILE MANY EXCITING ADVANCES ARE BEING MADE IN BIOTECHNOLOGY TODAY, IT IS NOT A NEW PHENOMENON. IN FACT, BIOTECHNOLOGY HAS A LONG HISTORY. A CENTURY AGO, LOUIS PASTEUR WAS ENGAGED IN RESEARCH THAT PROFOUNDLY CHANGED THE COURSE OF THE BIOSCIENCES AND MEDICINE. WE SOMETIMES FORGET HOW INDUSTRY WAS ALSO A DIRECT OBJECT OF A SUBSTANTIAL PORTION OF PASTEUR'S WORK. PERHAPS THE BEST WAY TO DESCRIBE THIS RELATIONSHIP IS TO CITE THE ENTRY ON PASTEUR IN THE ENCYCLOPEDIA BRITANNICA, WHERE HIS ACCOMPLISHMENTS ARE SUMMARIZED IN THE FOLLOWING SENTENCE. "PASTEUR PROVED THAT MICROORGANISMS CAUSE

FERMENTATION AND DISEASE; HE ORIGINATED AND WAS THE FIRST TO USE VACCINES FOR RABIES, ANTHRAX, AND CHICKEN CHOLERA; HE SAVED THE WINE, BEER AND SILK INDUSTRIES OF FRANCE AND ELSEWHERE; HE PERFORMED IMPORTANT PIONEER WORK IN STEREOCHEMISTRY; (AND) HE ORIGINATED PASTEURIZATION."[4]

A SIMILAR MODERN VERSION OF THIS CATALOG OF ACCOMPLISHMENTS COULD BE WRITTEN ABOUT THE RESULTS OF BASIC RESEARCH ON MOLECULAR BIOLOGY.

FOR ITS PART, THE NIH WOULD BE ENTHUSIASTIC ABOUT THE CONCEPTS AND METHODOLOGIES OF THE SCIENCE BASE SUPPORTING BIOTECHNOLOGY EVEN IN THE ABSENCE OF THE COMMERCIAL PROMISE. FOR THIS NEW SCIENCE HAS ADVANCED OUR UNDERSTANDING OF BIOLOGICAL MECHANISMS AND PROCESSES IN HEALTH AND DISEASE IN WAYS THAT ARE UNPRECEDENTED. NOW, THANKS TO LABORATORY TECHNIQUES SUCH AS RECOMBINANT DNA, WE ARE BEGINNING TO MAKE HEADWAY TOWARD EFFECTIVE VACCINE DEVELOPMENT IN SEVERAL RECALCITRANT FIELDS. THIS IS BUT ONE EXAMPLE. BIOTECHNOLOGY HAS HAD AN IMPACT ON THE CONDUCT OF BASIC BIOMEDICAL RESEARCH COMPARABLE PERHAPS TO THAT OF THE COMPUTER ON INFORMATION PROCESSING. BIOTECHNOLOGY HAS MOVED US AHEAD BY LEAPS AND BOUNDS IN UNDERSTANDING CANCER, GENETIC DEFECTS, ORGAN TRANSPLANTATION BIOLOGY, CLINICAL IMMUNOLOGY AND THE ALLERGIC RESPONSE, AND BONE DEVELOPMENT AND REPAIR, JUST TO NAME A FEW AREAS.

NIH CONTINUES TO MAKE A MAJOR COMMITMENT TO THE FUTURE OF BIOTECHNOLOGY. THE PROPORTION OF THE NIH BUDGET DEVOTED TO BIOTECHNOLOGY HAS REMAINED ESSENTIALLY CONSTANT FOR THE PAST FIVE YEARS, WITH ABOUT 11 PERCENT DEVOTED TO DIRECTLY RELATED RESEARCH, AND ABOUT 25 PERCENT DEVOTED TO UNDERLYING BASIC RESEARCH AND RESEARCH TRAINING.

BY BASIC RESEARCH DIRECTLY RELATED TO OR UTILIZING THE NEW BIOTECHNOLOGY, WE MEAN GENETIC MANIPULATION, CLONING OF DNA, USE OF SPECIAL TECHNIQUES TO ISOLATE AND DETECT DNA, CREATION OF HYBRIDOMAS AND PRODUCTION OF MONOCLONAL ANTIBODIES, AND COMPUTER METHODS USED TO ANALYZE DNA AND PROTEIN SEQUENCES. BASIC RESEARCH UNDERLYING THE NEW BIOTECHNOLOGY INCLUDES UNDIFFERENTIATED, FREE-RANGING INVESTIGATIONS IN GENETICS AND MOLECULAR BIOLOGY, CELL BIOLOGY AND IMMUNOLOGY.

IF 20 YEARS AGO THE DIRECTOR HAD TALKED OF THE NIH ROLE WITH RESPECT TO BIOTECHNOLOGY AS I HAVE DONE, IT IS LIKELY THAT THE DISCUSSION WOULD HAVE BEEN CONSIDERED INAPPROPRIATE, OR AT BEST SPECULATIVE. YET, AT THAT TIME, MUCH OF THE SCIENCE BASE ON WHICH THE NEW TECHNOLOGY DEPENDS HAD BEEN OR WAS BEING DISCOVERED IN THE COURSE OF CUSTOMARY RESEARCH ACTIVITIES.

IN DECEMBER 1985, AT MY SUGGESTION, THE NIH'S PRINCIPAL ADVISORY COMMITTEE SET ASIDE A TWO-DAY MEETING TO DISCUSS IN A PUBLIC FORUM THE PROPER ROLE FOR THE NIH IN THE ARENA OF

BIOTECHNOLOGY POLICY. THE GROUP'S CONSENSUS COULD VERY WELL APPLY AS WELL TO A RESEARCH-ORIENTED ACADEMIC INSTITUTION. THE ADVICE WAS TO CONTINUE TO DO WHAT WE DO BEST, THAT IS, CONTINUE TO CONDUCT AND SUPPORT RESEARCH AND RESEARCH TRAINING.

THAT CONCLUSION WAS SIMILAR TO ONE REACHED AT ABOUT THE SAME TIME BY THE PRESIDENT'S SCIENCE ADVISOR, GEORGE KEYWORTH, FOLLOWING A REVIEW OF FEDERAL SCIENCE POLICY. HE REPORTED, "PERHAPS THE MOST IMPORTANT ELEMENT OF POLICY THAT EMERGED FROM RECENT REASSESSMENTS WAS A RENEWED--AND CONSIDERABLY STRENGTHENED FEDERAL SUPPORT FOR BASIC RESEARCH. ....QUITE SIMPLY, BASIC RESEARCH IS A VITAL UNDERPINNING FOR OUR NATIONAL WELLBEING."[5]

IN SUPPORT OF THIS ASSERTION ABOUT THE IMPORTANCE OF BASIC RESEARCH TO THE NATION, DR. KEYWORTH OFFERED ADVICE THAT IS AS APPLICABLE TO ISRAEL AND TEL AVIV UNIVERSITY AS IT WAS TO THE UNITED STATES. HE URGED THE SUPPORT OF INSTITUTIONS OF HIGHER LEARNING FOR RESEARCH AND THE TRAINING OF NEW TALENT FOR TECHNOLOGICAL LEADERSHIP AND FOR THE GENERATION OF NEW KNOWLEDGE TO DRIVE ECONOMIC GROWTH.

A MORE COMPREHENSIVE STATEMENT OF THE MANY ROLES OF SCIENCE IN OUR SOCIETY APPEARS IN AN INSCRIPTION ON THE DOME OF THE GREAT HALL OF THE NATIONAL ACADEMY OF SCIENCES IN WASHINGTON. IT READS, "....TO SCIENCE: PILOT OF INDUSTRY, CONQUEROR OF DISEASE, MULTIPLIER OF THE HARVEST, EXPLORER OF

THE UNIVERSE, REVEALER OF NATURE'S LAW AND ETERNAL GUIDE TO TRUTH."

I TRUST THAT MY REMARKS, EVEN THOUGH THEY HAVE FOCUSED ON THE BIOSCIENCES, HAVE CARRIED WITH THEM IMPLICATIONS OF THE SEARCH FOR TRUTH THAT GOES ON IN ALL OF THE DISCIPLINES REPRESENTED BY THE HONOREES, AND BY THE UNIVERSITY. ONCE AGAIN, ON BEHALF OF ALL WHO HAVE BEEN SO SIGNALLY HONORED TODAY, OUR MOST SINCERE THANKS.

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OPENING REMARKS
AND
INTRODUCTION OF DR. FRANCOIS JACOB*

BY
JAMES B. WYNGAARDEN, M.D.**

THIS IS INDEED A RARE OCCASION, A MEMORABLE TIME FOR EACH OF US. I AM HONORED AND PRIVILEGED TO WELCOME YOU TO THIS CENTENARY SYMPOSIUM SPONSORED JOINTLY BY THE PASTEUR INSTITUTE AND THE NATIONAL INSTITUTES OF HEALTH IN OBSERVANCE OF THEIR COMMON HUNDREDTH ANNIVERSARY.

I EXTEND A SPECIAL WELCOME TO EACH OF THE DISTINGUISHED SCIENTISTS WHO WILL PARTICIPATE IN THE DISCUSSIONS THAT ARE TO FOLLOW. THE SUBJECT TO BE ADDRESSED IN THE SYMPOSIUM IS AT THE FOREFRONT OF SCIENCE TODAY. MOLECULAR BIOLOGY IS AT THE FOCUS OF SUBSTANTIAL ATTENTION IN BOTH OUR INSTITUTIONS AT THIS TIME, IN MUCH THE SAME WAY THAT PASTEUR'S IDEAS ON PATHOGENIC AGENTS WERE AT THE FOREFRONT IN 1887. IT IS PROBABLE THAT OUR ATTENTION WILL BE GIVEN MORE TO THE FUTURE THAN TO THE PAST AS WE CONSIDER THE CHALLENGING SUBJECT "THE IMPACT OF MOLECULAR BIOLOGY ON BIOMEDICAL RESEARCH," BUT INASMUCH AS THIS IS A CENTENNIAL OCCASION, I WILL REFER BRIEFLY TO A BIT OF HISTORY WE HAVE IN COMMON.

JUST OVER 100 YEARS AGO, THE UNITED STATES WAS IN THE GRIP OF FEAR THAT THE CHOLERA PANDEMIC OF 1881 MIGHT BE IMPORTED FROM OVERSEAS. THIS CONCERN PROMPTED HEALTH AUTHORITIES TO SEND A YOUNG AMERICAN DOCTOR, JOSEPH KINYOUN, TO STUDY WITH PASTEUR AND KOCH IN THE HOPE THAT INSIGHTS FROM THE LABORATORIES OF THESE GIANTS MIGHT SUGGEST MEANS FOR PREVENTING A WAVE OF CHOLERA IN THE UNITED STATES. UPON DR. KINYOUN'S RETURN HE SET UP A BACTERIOLOGICAL LABORATORY IN 1887 CALLED THE LABORATORY OF HYGIENE AT THE MARINE HOSPITAL ON STATEN ISLAND, NEW YORK. THE NATIONAL INSTITIUTES OF HEALTH IS THE LINEAL DESCENDANT OF THAT ONE ROOM LABORATORY.

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*PRESENTED AT THE NIH-PASTEUR INSTITUTE CENTENNIAL SYMPOSIUM, BETHESDA, MARYLAND, MAY 26, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

ALTHOUGH BOTH OF THE ORGANIZATIONS SPONSORING THIS SYMPOSIUM WERE FOUNDED IN 1887, THEY DIFFERED MARKEDLY IN THEIR EARLY YEARS. THE PASTEUR INSTITUTE WAS A SUBSTANTIAL ORGANIZATION AT THE TIME ITS FOUNDING WAS ANNOUNCED, BUT THE LABORATORY OF HYGIENE WAS, IN ESSSENCE, A FRAGILE TRANSPLANT OF EUROPEAN SCIENCE ON THIS SIDE OF THE ATLANTIC. MEDICAL SCIENCE IN THE UNITED STATES LAGGED FAR BEHIND THE STATE OF KNOWLEDGE IN EUROPE. IT WAS FOR THIS REASON THAT SHORTLY AFTER THE LABORATORY OF HYGIENE WAS ESTABLISHED OUR FOUNDING DIRECTOR, DR. KINYOUN, RETURNED TO PARIS FOR FURTHER STUDY AND CONSLUTATION AT THE PASTEUR INSTITUTE.

THROUGH THE INTERVENING YEARS NUMEROUS LINKAGES HAVE BEEN INITIATED AND MAINTAINED BETWEEN AMERICAN SCIENTISTS AND THEIR COLLEAGUES IN FRANCE, PARTICULARLY AT THE PASTEUR INSTITUTE. THE HIGH QUALITY OF BASIC RESEARCH PERFORMED BY TOP SCIENTISTS AT PASTEUR HAS BEEN RESPONSIBLE NOT ONLY FOR BRINGING INTERNATIONAL RECOGNITION AND THE HIGHEST HONORS IN SCIENCE TO THE INVESTIGATORS, IT HAS FOSTERED A HIGH LEVEL OF EXCITEMENT OVER A LONG PERIOD OF TIME WITHIN THE EUROPEAN RESEARCH COMMUNITY, AND ESPECIALLY IN PARIS. EARLY IN MY ACADEMIC CAREER I SOUGHT AND WAS GIVEN AN OPPORTUNITY TO SPEND A YEAR IN PARIS IN THE STIMULATING SCIENTIFIC ENVIRONMENT THERE, (ONE OF THE CHIEF ATTRACTIONS, AS FAR AS I WAS CONCERNED, WAS THE OPPORTUNITY TO ASSOCIATE WITH FRANCOIS GROS, WHO I AM DELIGHTED TO SAY WILL BE A PARTICIPANT IN THIS SYMPOSIUM.)

IN A MOMENT I WILL PRESENT TO YOU THE CHAIRMAN OF THE BOARD OF THE PASTEUR INSTITUTE, WHO PERSONALLY HAS CONTRIBUTED MUCH TO THE SCIENTIFIC EXCITEMENT AND PROGRESS OF OUR TIME.

FRANCOIS JACOB BEGAN STUDYING MEDICINE AT THE FACULTY OF PARIS WITH THE INTENTION OF BECOMING A SURGEON, BUT HIS STUDIES WERE INTERRUPTED BY THE WAR. IN HIS SECOND YEAR IN MEDICAL SCHOOL HE JOINED THE FREE FRENCH IN LONDON AND SAW ACTION AS A MEDICAL OFFICER IN AFRICA, WHERE HE WAS WOUNDED. LATER, WHILE POSTED WITH THE SECOND ARMOURED DIVISION IN NORMANDY, AUGUST 1944, HE WAS SEVERELY WOUNDED. AFTER THE WAR HE COMPLETED HIS MEDICAL STUDIES AND SUBMITTED HIS DOCTORAL THESIS IN PARIS IN 1947. HE TURNED TO BIOLOGY AND OBTAINED A DOCTORATE IN SCIENCE IN 1954 AT THE SORBONNE.

HE HAD JOINED THE PASTEUR INSTITUTE IN 1950 TO WORK UNDER DR. ANDRE LWOFF. HE WAS APPOINTED LABORATORY DIRECTOR IN 1956 AND THEN IN 1960 HEAD OF THE DEPARTMENT OF CELL GENETICS. IN 1964 HE WAS ALSO APPOINTED PROFESSOR OF CELL GENETICS AT THE COLLEGE DE FRANCE. AT THIS TIME HE IS CHAIRMAN OF THE BOARD OF THE PASTEUR INSTITUTE.

DR. JACOB HAS WORKED MAINLY ON THE GENETIC MECHANISMS OF BACTERIA AND BACTERIAL VIRUSES, AND ON THE INFORMATION TRANSFER AND REGULATORY SYSTEMS IN THE BACTERIAL CELL.

HE IS AN AUTHOR OF NOTE. HIS MOST RECENT BOOKS ARE ONE PUBLISHED IN 1981 TITLED "THE POSSIBLE AND THE ACTUAL, A VIEW ON EVOLUTION AND ITS MECHANISMS," AND ANOTHER PUBLISHED RECENTLY (IN 1987) THAT IS AN AUTOBIOGRAPHY TITLED "LA STATUE INTERIEURE."

DR. JACOB HAS RECEIVED MANY HONORS, INCLUDING HIS ELECTION TO THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, THE AMERICAN ACADEMY OF ARTS AND SCIENCES, AND SIMILARLY DISTINGUISHED ORGANIZATIONS IN A NUMBER OF COUNTRIES OF WESTERN EUROPE. IN 1965, JOINTLY WITH ANDRE LWOFF AND JACQUES MONOD HE WAS AWARDED THE NOBEL PRIZE FOR PHYSIOLOGY OR MEDICINE IN RECOGNITION OF THEIR WORK THAT CAST NEW LIGHT ON CELLULAR GENETICS.

IT IS WITH REAL PLEASURE THAT I PRESENT DR. FRANCOIS JACOB.

NOTES FOR NLM BOARD OF REGENTS MEETING*

BY

JAMES B. WYNGAARDEN, M.D.**

THE CENTENNIAL

SINCE I LAST REPORTED TO THE BOARD OF REGENTS, A NUMBER OF CENTENNIAL EVENTS HAVE TAKEN PLACE AND PLANNING IS ADVANCING FOR MAJOR EVENTS THIS FALL.

- ONE OF THE HIGHLIGHT EVENTS OF THE YEAR IS THE CENTENARY SYMPOSIUM ON "THE IMPACT OF MOLECULAR BIOLOGY ON BIOMEDICAL RESEARCH" BEING HELD THIS WEEK IN THE MASUR AUDITORIUM HERE. WHAT MAKES THIS EVENT SPECIAL IS THE FACT THAT IT IS IN EFFECT A JOINT CELEBRATION OF THE 100TH BIRTHDAY OF THE NATIONAL INSTITUTES OF HEALTH AND THE PASTEUR INSTITUTE, BOTH OF WHICH WERE FOUNDED IN 1887.

- THE CENTENNIAL SCHOLARS AND TEACHERS WEEKEND PROGRAM WAS HELD FEBRUARY 28-MARCH 3. ALL STATES PLUS AMERICAN SAMOA, GUAM, NORTHERN MARIANA ISLANDS, PUERTO RICO, THE VIRGIN ISLANDS AND THE DISTRICT OF COLUMBIA WERE REPRESENTED.

- TWO OF THE SEVEN CONGRESSIONAL BREAKFASTS HAVE BEEN HELD. WELL RECEIVED BY IMPORTANT CONGRESSIONAL MEMBERS AND STAFFERS. OUTSTANDING PROGRAMS--(E.G., AT APRIL 24 PROGRAM SPEAKERS INCLUDED TWO NOBELISTS, ARTHUR KORNBERG AND STANLEY COHEN).

- FIVE THOUSAND RADIO STATIONS AROUND THE COUNTRY HAVE RECEIVED AND ARE USING 20-PART CENTENNIAL TAPED PUBLIC SERVICE ANNOUNCEMENT "SALUTES."

- COMPLETE PRESS KITS SENT NATIONWIDE TO REPORTERS AND OTHERS (4,000 PLUS).

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*REMARKS TO THE NATIONAL LIBRARY OF MEDICINE BOARD OF REGENTS, BETHESDA, MARYLAND, MAY 28, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

- SHOOTING PROGRESSING ON SCHEDULE ON PBS TV SERIES.

- DOUBLEDAY AND COMPANY WILL PUBLISH COMMEMORATIVE BOOK AS COMPANION TO TV SERIES.

- A NUMBER OF "SATELLITE" CENTENNIAL OBSERVANCES BEING HELD IN DIFFERENT PARTS OF THE COUNTRY. THE NIH DIRECTOR HAS MADE SOME 40 ADDRESSES RELATED TO CENTENNIAL OBSERVANCES SINCE OCTOBER. MORE SATELLITE OBSERVANCES TO COME.

- PLANNING PROCEEDING FOR MAJOR SYMPOSIUM, ALUMNI REUNION, AND OPEN HOUSE TO CLIMAX CENTENNIAL YEAR, OCTOBER 15-18.

STATUS OF 1988 APPROPRIATIONS

HOUSE ACTION ON THE 1987 SUPPLEMENTAL APPROPRIATIONS SPECIFICALLY REJECTED PRESIDENT'S PROPOSAL ABOUT EXTENDING AVAILABILITY OF 1987 FUNDS INTO 1988. SENATE ACTION EXPECTED THIS WEEK.

MARKUP OF 1988 APPROPRIATION IN HOUSE SUBCOMMITTEE ESTIMATED BY END OF SECOND WEEK OF JUNE. SENATE SUBCOMMITTEE HAS SAID WILL MARKUP BEFORE END OF MONTH.

THE OVERALL BUDGET RESOLUTION IS IN CONFERENCE. FROM THE RESOLUTION'S LEVELS IT APPEARS THAT NIH APPROPRIATION WILL BE RECOMMENDED WELL BEYOND PRESIDENT'S BUDGET. UNOFFICIAL ESTIMATES FROM $6.5 BILLION UP.

SEQUENCING THE HUMAN GENOME

TWO PROGRAM ANNOUNCEMENTS ON SEQUENCING THE HUMAN GENOME WERE PUBLISHED IN THE MAY 29 NIH GUIDE TO GRANTS AND CONTRACTS. THE INTEREST IS NIH-WIDE WITH ALL BIDS PARTICIPATING.

- THE FIRST PROGRAM ANNOUNCEMENT'S PURPOSE IS TO ENCOURAGE RESEARCH IN AND DEVELOPMENT OF METHODS FOR CHROMOSOME MAPPING AND DNA SEQUENCING.

- THE SECOND ANNOUNCEMENT IS INTENDED TO STIMULATE NEW RESEARCH IN COMPUTER HANDLING OF INFORMATION GENERATED IN LABORATORIES.

TWO WEEKS AGO NICHD HELD A WORKSHOP FOR GRANTEES CURRENTLY WORKING ON CHROMOSOME 21 WITH SPECIAL REFERENCE TO DOWN'S SYNDROME AND ALZHEIMER'S DISEASE.

ON MAY 8 THE FIRST MEETING OF THE SUBCOMMITTEE ON THE HUMAN GENOME OF THE WORKING GROUP ON BIOTECHNOLOGY OF THE WHITE HOUSE DOMESTIC COUNCIL. SUBCOMMITTEE INCLUDES REPRESENTATION FROM DOE, NSF, FDA, EPA, USDA, AND CHAIRED BY NIH.

IN OCTOBER 1986 THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH, ADDRESSED THE POTENTIAL ROLE OF NIH WITH REGARD TO SEQUENCING THE HUMAN GENOME. LEADING EXPERTS PARTICIPATED AND FOUR MAIN CONCLUSIONS WERE REACHED:

- FIRST, METHODS FOR HANDLING THE VAST AMOUNT OF INFORMATION BEING GENERATED BY EXISTING SEQUENCING ACTIVITIES NEED TO BE EXPANDED AND SUPPORTED MORE ADEQUATELY.

- SECOND, THAT THERE IS NEED FOR CONSIDERABLE IMPROVEMENT IN METHODS.

- THIRD, THAT COMPLETE PHYSICAL AND GENETIC MAPS OF THE HUMAN GENOME SHOULD BE DEVELOPED AS RAPIDLY AS POSSIBLE.

- FOURTH, SEQUENCING OF THE HUMAN GENOME IS A LAUDABLE SCIENTIFIC OBJECTIVE OF POTENTIALLY IMMENSE IMPORTANCE, BUT THAT FOR THE PRESENT WE SHOULD CONCENTRATE ON SEQUENCING GENES OF SPECIAL BIOLOGICAL INTEREST. IN GENERAL, THE COMMITTEE FELT THAT AN ALL OUT EFFORT SHOULD AWAIT FURTHER DEVELOPMENTS. THEY ALSO RECOMMENDED THAT THE INCREMENTAL COSTS OF THE SEQUENCING SHOULD BE MET BY NEW MONIES SO AS NOT TO COMPETE WITH OTHER RESEARCH. IT IS MY BELIEF THAT SUCH MONEY WILL NOT BE FORTHCOMING FROM GOVERNMENT FUNDS. IF, HOWEVER, THE PRESENT COST OF SEQUENCING OF ABOUT $1 PER NUCLEOTIDE CAN BE REDUCED THROUGH ADVANCES BY A FACTOR OF TEN, THE PRIORITY ISSUES WILL BE LESS DIFFICULT.

ANTIVIRALS-AIDS INITIATIVE

NIH IS USING THE TECHNIQUES OF A RELATIVELY NEW FIELD, STRUCTURAL BIOLOGY IN A SPECIAL EFFORT TO DEVELOP ANTIVIRAL DRUGS INCLUDING, FIRST OF ALL, ONE THAT WILL TARGET THE AIDS MACROMOLECULE.

THE NIH PROGRAM INCLUDES THE NIAID/NCI NATIONAL COOPERATIVE DRUG DISCOVERY GROUP FOR THE TREATMENT OF AIDS (INITIATED IN 1986).

NIAID HAS ALSO INVITED AP CATIONS FOR REGULAR RESEARCH GRANTS TO DETERMINE THE THREE-DIMENSIONAL STRUCTURE OF THE ENVELOPE GLYCOPROTEINS, REVERSE TRANSCRIPTASE, AND OTHER COMPONENTS OF THE AIDS VIRUS.

NIGMS IS ALSO INVOLVED IN THE PROGRAM. IT HAS PUBLISHED AN RFA ANNOUNCING THE AVAILABILITY OF FUNDS FOR THE EXTRAMURAL COMPONENT OF THE PROGRAM. WE HOPE THAT IT WILL STIMULATE ORGANIZATION OF MULTIDISCIPLINARY RESEARCH GROUPS THAT WILL INVESTIGATE THE STRUCTURE OF VIRAL PROTEINS AND ALSO STIMULATE THE TRAINING OF GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS.

BIG SCIENCE

THE ISSUE OF SEQUENCING, AND THE DECISION TO ESTABLISH A LIMITED NUMBER OF STRUCTURAL BIOLOGY CENTERS FOR THE MINUTE EXPLORATION OF THE AIDS VIRUS AND THE DEVELOPMENT OF ANTIVIRAL AGENTS, HAVE GENERATED A HEIGHTENED INTEREST IN THE QUESTION OF BIG SCIENCE IN BIOLOGY. THE NIH HAS TAKEN A FEW STEPS IN THAT DIRECTION WITH PROGRAM PROJECT GRANTS AND CENTER AWARDS, BUT THE DOMINANT MECHANISM REMAINS THE INVESTIGATOR-INITIATED RESEARCH PROJECT GRANT.

THE HOWARD HUGHES MEDICAL INSTITUTE IS BEGINNING TO FUND LARGE UNITS WITH SPECIFIC PROGRAM ORIENTATION IN SOME 20 OR MORE LEADING INSTITUTIONS, WITH GENEROUS SUPPORT AND MAXIMUM FLEXIBILITY.

THE ROLE OF BIG SCIENCE IN BIOLOGICAL RESEARCH HAS NOT BEEN ADDRESSED AS A PUBLIC POLICY QUESTION. THE TOPIC IS SCHEDULED TO RECEIVE THE ATTENTION OF A STUDY TO BE CONDUCTED BY THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES, AND PARTLY FINANCED BY THE NIH.

PROGRESS ON ALZHEIMER'S DISEASE

THIS SPRING CRITICAL FINDINGS WERE ANNOUNCED THAT MANY BELIEVE COULD HELP LEAD TO DISCOVERY OF THE CAUSE OF ALZHEIMER'S DISEASE. THIS DISORDER AFFECTS AN ESTIMATED 2.5 MILLION OLDER AMERICANS, AND IS THE FOURTH LEADING CAUSE OF DEATH IN DEVELOPED COUNTRIES.

ONE ANNOUNCEMENT CONCERNED FINDINGS FROM WHICH IT CAN BE INFERRED THAT THERE IS A GENE IN A RELATIVELY RESTRICTED REGION OF CHROMOSOME 21 THAT CAUSES ALZHEIMER'S DISEASE IN MEMBERS OF THOSE FAMILIES THAT INHERIT THE DEFECTIVE GENE. KNOWING THE APPROXIMATE LOCATION OF THE "ALZHEIMER'S SUSCPTIBILITY GENE" ON CHROMOSOME 21 MAKES IT FEASIBLE TO ATTEMPT TO ISOLATE IT AND FIND OUT HOW IT CAUSES THE DISEASE.

THE SECOND ANNOUNCEMENT WAS THAT NIH SCIENTISTS, IN COLLABORATION WITH A FRENCH TEAM, HAVE FOUND THAT NONFAMILIAL ALZHEIMER'S DISEASE PATIENTS AND DOWN'S SYNDROME PATIENTS HAVE AN ABNORMAL NUMBER OF COPIES OF THE GENE THAT MAKES AMYLOID PROTEIN, A SUBSTANCE ASSOCIATED WITH DEGENERATIVE BRAIN GHANGES IN ALZHEIMER'S DISEASE. IN BOTH GROUPS OF PATIENTS STUDIED THE ABNORMAL GENE DUPLICATION OCCURS IN THE SAME CRITICAL SEGMENT OF CHROMOSOME 21, WHICH HAD BEEN IMPLICATED IN DOWN'S SYNDROME.

THESE FINDINGS, AS WELL AS OTHER RECENT PROGRESS IN UNDERSTANDING SPECIFIC PATHOLOGIC CHANGES CAUSED BY ALZHEIMER'S DISEASE, MARK WHAT IS, IN FACT, A RADICAL INCREASE IN KNOWLEDGE ABOUT THIS DISORDER.

Joseph Goldberger and the Conquest of Pellagra*

by

James B. Wyngaarden, M.D.**

It is a daunting experience to examine the list of those who have addressed the Gold Headed Cane Society, daunting, that is, for one who has been asked to do what I am about to do. I am deeply honored to have been invited to join such a distinguished company. I will admit to more than a little curiosity about some of the subjects addressed here previously. What could Dr. Roger I. Lee have said under the titled "Alas Poor Yorick! I Knew Him Horatio"; or what did Dr. J. Englebert Dunphy convey in his address on "Caning, Streaking, and the Pursuit of Happiness"? Even my longtime friend Holly Smith used a Delphic title for his address here last year. Did he really mean that "Caning is Good for You"?

As I considered what would be an appropriate subject, it seemed to me that my choice must relate in some way to the 100th anniversary of the National Institutes of Health.

Having made the decision to address some chapter in the history of our unusual organization, the rest was easy. I would talk about Joseph Goldberger and the Conquest of Pellagra. For he was a true hero of American Medicine whose alertness and willingness to challenge widely held opinion led to a most gratifying medical accomplishment--the discovery of a simple, safe, and effective means for the cure and prevention of a serious disease. His work in solving the riddle of pellagra in the U.S. ranks today as one of the outstanding epidemiological achievements of this century. His career spanned 30 years, from 1899 until his untimely death from cancer in 1929. Goldberger made significant contributions to the understanding of yellow fever, typhoid fever, dengue, measles and diptheria prior to his work on pellagra--a disease that had plagued and puzzled man from the earliest of times. The story is a chapter of our institutional history in that, Dr. Goldberger, during practically all of his professional career, was associated with the Public Health Service Hygienic Laboratory, that in time became the National Institues of Health.

But before telling you more about this remarkable man and his achievement, let me say a few words about the NIH.

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*The William J. Kerr Lecture Presented to the Gold-Headed Cane Society's Annual Dinner, San Francisco, California, May 29, 1987

**Director, National Institutes of Health, Bethesda, Maryland

The Laboratory had its beginning when young Dr. Joseph Kinyoun was sent to Europe in the early 1880s to study with Pasteur and Koch in the hope that he could learn measures for protecting the United States from the threatened importation of cholera. Upon his return Dr. Kinyoun, in August 1887, set up a one-room bacteriological laboratory in the attic of the Marine Hospital Service Facility on Staten Island, New York.

First called the Laboratory of Hygiene and later the Hygienic Laboratory, this modest Federal facility was moved to Washington where it occupied a floor of an existing government building on Capitol Hill. The move to Washington was significant in that it signaled a broader role for the laboratory than as an adjunct to quarantine activities at a port of entry. The Laboratory began to be a national resource.

In 1904 it was moved to newly constructed buildings in Washington near what is now the Kennedy Center. The buildings were the home of the laboratory for 35 years. In 1930 the Hygienic Laboratory became the National Institute of Health. Until World War II the NIH was a small Federal laboratory with little organizational contact outside of government circles. At the end of the war, however, in 1945, the agency was given the responsibility for administering grants awarded to academic institutions, hospitals and other laboratories throughout the Nation. Thus began a time of spectacular growth for the agency. The current budget is $6.2. Of that amount more than $600 million is allocated to research in the agency's own laboratories. These in-house or intramural laboratories are direct descendants of the laboratories in which Joseph Goldberger conducted his studies, beginning just before the turn of the century and ending in 1929.

Joseph Goldberger was born in Czechoslovakia in 1874 on a peasant tenant farm. He was brought to New York City when he was seven, where his father opened a grocery store on the Lower East Side. When he was sixteen the career choice of this determined delivery boy was to be a civil engineer but, after hearing the Harvey Lecture given by a Bellevue Hospital College physician, he decided to switch to medicine.

I wish our records included the name of the lecturer who probably never knew how much he had accomplished by igniting the enthusiasm of young Joseph Goldberger for a career in medicine. He graduated second in his class at Bellevue, where he acquired a reputation as a hater of routine but a master of case history writing. It was said that, "To him every case was a great and absorbing mystery, the solution to an exciting challenge."

He tried private practice but after two years decided that it was not his field and he entered the Marine Hospital Service in 1899 at the age of 25. That was only 12 years after the NIH had its beginning in the Marine Hospital on Staten Island.

Goldberger performed brillant and courageous work on typhus fever operating always at the epidemic scene. He also made important studies of the Mexican form of typhus and yellow fever. His greatest contribution and challenge, however, came when he was put in charge of pellagra investigations.

Pellagra was then prevalent in rural areas of the South, but was considered a problem in 40 States, particularly in prisons and other State

run institutions that housed inmates for long periods of time. In 1912 Surgeon General Rupert Blue said of pellagra, "When consideration is given to the nature of the disease, its chronicity and termination often in invalidism, insanity or death, the lack of definite knowledge as to its causation and transmission, the unsatisfactory results of treatment, its rapid and continuous spread, the class of people affected, and the uneasy state of the public mind in many places, then the thorough investigation of this mysterious disease assumes immediate importance." (The statement had many of the same elements of urgency later associated with AIDS.)

The Public Health Service was determined to make an attack on pellagra. This determination was likely reinforced by the widespread assumption that pellagra was an infectious disease related in some way to the sanitary condition of rural southern homes or in the facilities where inmates were held. A special appropriation was made to the Public Health Service in 1914 providing $47,000 to set up a special laboratory for study of pellagra. On February 14, 1914, Dr. Joseph Goldberger was put in charge of the investigations with headquarters at the Hygienic Laboratory in Washington. He was 40 years old at the time.

By mid-1914 Dr. Goldberger's review of existing information on the problem, plus a limited amount of personal observation, caused him to take public issue with the widespread assumption that pellagra was a communicable disease. The June 26, 1914 edition of Public Health Reports carried his paper titled, "The Etiology of Pellagra--The Significance of Certain Epidemiological Observations with Respect Thereto." One can sense the excitement of the chase in the constrained first sentence--"The writer desires to invite attention to certain observations recorded in the literature of pellagra the significance of which appears entirely to have escaped attention." The observations were of the staffs of the custodial institutions where many inmates either had pellagra on admission or developed it there. He recited the histories of institution after institution where the ward personnel, nurses and attendants spent a substantial amount of time in close association with the pellagrins yet appeared universally to be immune . He then asked the telling question, "If pellagra be a communicable disease, why should there be this exemption of the nurses and attendants?" He commented that "this peculiar exemption or immunity is inexplicable on the assumption that pellagra is communicable."

He concluded that the only difference that could account for the apparent immunity was in the diets of the two groups. The same differences appeared to exist between the rural poor who were susceptible to pellagra and their contemporaries in the large cities who were not.

That conclusion, however was only the beginning, and in the June 14 report with remarkable insight he wrote," The writer is satisfied that the consumption of corn or corn products is not essential to the production of pellagra, but this does not mean that corn, the best of corn, or corn products, however, nutritious and however high in caloric value they may be, are not objectionable when forming of themselves or in combination with other cereals and with vegetables, a large part of the diet of the individual."

"In view of the great uncertainty that exists as to the true cause of pellagra, it may not be amiss to suggest that pending the final solution of this problem it may be well to attempt to prevent the disease by improving

the dietary of those among whom it seems most prevalent. In this direction I would urge the reduction in cereals, vegetables, and canned foods that enter to so large an extent into the dietary of many of the people in the South and an increase in the fresh animal food component, such as fresh meats, eggs, and milk."

Much of the remainder of Dr. Goldberg's life was dedicated to finding that "true cause" and "final solution."

Dr. Goldberger's confirmatory investigations were classics of epidemiology. He was a master of observation and experimentation. Goldberger and his associates showed that the poor monotonous diets common to many low income people--diets high in carbohydrate and low in good quality protein and fresh vegetables--induced pellagra. In public institutions where the disease occurred, these investigators demonstrated that generous amounts of milk, eggs, meat, beans and peas prevented it. Yet, physicians who were treating pellagra at the time strongly believed that it was caused by an infectious organism and would not accept Goldberger's evidence.

To counter this skepticism, and to offer proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later, Goldberger and his four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife, Mary. None contracted the disease, though there is no record as to what adverse symptoms may have resulted from these heroic experiments.

Mere recitation of these events and conclusions does not do justice to Goldberger. He becomes alive in his handwritten diary, written by him during 1914-15 trek through orphanages, lumber camps, asylums, prisons, hospitals, anhd other areas in the south where pellagra was rampant. He inquired into water supplies, sewage disposal and insect screening and became more and more convinced that diet was the cause of this dread disease. Now he had to prove that skin eruptions, diarrhea and mental deterioration, characteristic of pellagra, were not caused by an infectious etiology. He proved this with the help of convicts in Mississippi. After signing "informed consents," 12 convict volunteers happily agreed to a 6 month diet of biscuits, mush, grits, sirrup, coffee (no milk), corn bread, cabbage, sweet potatoes, rice and collards--all they wanted of these foods, but nothing else. Eighty (80) convicts served as controls. They ate the regular prison diet that was abundant with a variety of fresh foods. Within 5 months the convicts on the restricted diet had the red marks on their skin and were diagnosed by several experts as pellagrous. The volunteers were then pardoned and soon recovered--by eating a regular varied diet.

Goldberger persuaded the superintendants of many southern institutions to adopt his dietary changes. He convinced them that pellagra in the orphans and others could be prevented by eating adequate animal protein (eggs, milk, meat) and fresh vegetables

He later developed a treatment using yeast in the diet and by 1922 he knew that the amino acid tryptophane was crucially related to the cause of the disease. Goldberger had developed animal models of pellagra in dogs and rats as well as foods and extracts that would treat or prevent "black tongue" in

dogs. At the time of his death in January 1929, Dr. Goldberger had established that there was something that he called the pellagra-preventive factor that was probably a vitamin, but he had not isolated it. He knew which foods contained the factor and had developed lists of the foods for use in prescribing for people so as to prevent pellagra. He kept adding to these lists until he was no longer able to work.

In 1928 a 27-year-old physician-scientist, William Henry Sebrell, Jr., was assigned to assist Dr. Goldberger in his efforts to pinpoint the identity of the pellagra-prevention factor. Dr. Sebrell, who later would become the seventh director of the National Institutes of Health, 1950-1955, worked closely with Dr. Goldberger for the last eight months of the older scientist's life. Dr. Sebrell continued the pellagra project and was a close competitor in the final sprint that in 1936 led to the isolation of nicotinic acid as the pellagra-preventive factor by Conrad Elvehjem of the University of Wisconsin. The proof of the role of tryptophane in the synthesis of niacin had to wait until 1942, 20 years after Goldberger's recognition of the role in prevention of pellagra from his meticulous clinical investigations.

In retrospect it is hard to believe that scientists and physicians remained unconvinced about the nature of pellagra in the face of Goldberger's unassailable logic about the immunity of attending personnel, his heroic experiments involving his associates, his wife and himself, and his demonstration as to how to make pellagra disappear from custodial institutions by changing the diets afforded inmates.

The doubts about Goldberger's findings persisted and were not refuted until after his death. According to Dr. Sebrell, no less a personage than the then director of the Hygienic Laboratory, my predecessor, Dr. George McCoy doubted Goldberger's conclusions, telling the successor who took charge of the pellagra project that the question was yet open whether "pellagra is really a vitamin deficiency or an infection." But years before the resolution of the scientific questions, Goldberger's insights had led to measures that conquered pellagra.

Goldberger is an excellent example of what Walsh McDermott has called "statistical compassion." Goldberger apparently did not enjoy private medical practice. Comments about him by Sebrell and others suggest a rigid, forbidding and uncompromising nature, with the commitment of a driven man. These are not necessarily the best traits for the doctor-patient relationship or the bedside manner. But they were exactly the traits that the pellagra problem required. Goldberger lived just long enough to find the cause and the cure, and to lay the groundwork for definitive understanding and precise therapy.

Goldberger stands as one of the great creative scientists of the USPHS. First he examined the existing data. Then he drew his own conclusions. He exhibited the quality of all great scientists and physicians--intellectual skepticism--an irreverence, if you will, not for achievement, but for authoritarian dogma and conventional wisdom.

Having formulated a tentative conclusion, a new hypothesis, he set about through painstaking, even relentless observation and experimentation, to determine whether his novel insights were correct. And he conquered a disease that had been a leading cause of death in the rural impoverished south.

Has pellagra been eradicated? Almost! One still occassionally sees a "pellagrin," as they were once called, among the rural poor of North Carolina, e.g., but cases attributable to dietary deficiency alone are rare. Pellagra may complicate chronic alcoholism, or chemotherapy with 6-mercaptopurine (6MP) or isonicotinic acid hydrazide (INH). It may be the presenting clue to Hartnup's disease, an inborn error of neutral amino acid absorption, including tryptophane. Or it may complicate the malignant carcinoid syndrome in which dietary tryptophane is stolen for conversion to hydroxytryptamine, but these disorders are extraordinarily rare. Their occurrence does not gainsay the statement that pellagra has been cured. And for this we honor Joseph Goldberger. We in the USPHS take special pride in him in our Centennial year.

DRAFT SW

NOTES FOR "REPORT ON NIH ACTIVITIES*

BY

JAMES B. WYNGAARDEN, M.D.**

OPERATING BUDGET FOR FY 1987 AND APPROPRIATION FOR FY 1988

- THE PRESIDENT'S BUDGET REQUEST FOR FY 1988 INCLUDED THE PROPOSAL THAT $334 MILLION OF THE FUNDS PREVIOUSLY APPROPRIATED FOR NIH FOR 1987 BE WITHHELD FROM OBLIGATION DURING THE CURRENT YEAR AND BE USED FOR RESEARCH FUNDING NEXT YEAR IN FY 1988. SUCH AN ACTION REQUIRES CONGRESSIONAL APPROVAL. THE HOUSE OF REPRESENTATIVES HAS REJECTED THE PRESIDENT'S PROPOSAL AND THE SENATE IS EXPECTED TO TAKE THE SAME ACTION (IF IT HAS NOT ALREADY DONE SO).

- THUS NIH SPENDING AUTHORITY FOR 1987 IS $6.2 BILLION, THE AMOUNT SPECIFIED IN THE ORIGINAL APPROPRIATION FOR THE YEAR.

- FROM ACTIONS THAT HAVE BEEN TAKEN BY BOTH THE HOUSE AND SENATE WITH REGARD TO THE OVERALL BUDGET CEILING FOR THE GOVERNMENT, IT APPEARS THAT THE NIH APPROPRIATION FOR FY 1988 WILL EXCEED SUBSTANTIALLY THE PRESIDENT'S REQUEST. UNOFFICIAL ESTIMATES RANGE UPWARD FROM $6.5 BILLION.

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*PRESENTED AT THE 27TH MEETING OF THE STANDING COMMITTEE OF THE EUROPEAN MEDICAL RESEARCH COUNCIL (EMRC), BETHESDA, MARYLAND, JUNE 8-9, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

- When all types of awards are considered, the NIH during 1986 funded more than 28,000 projects involving approximately 50,000 scientists in more than 1,600 institutions. Within the total of awards 19,300 were made for project grants averaging a total cost of $151,847 per year.

- Expressed in constant dollars the average total cost of awards has been remarkably constant over the past 15 years. However, during this time the indirect cost component for all grant awards has increased from 21 percent to 31.4 percent of the total award and, accordingly, in constant dollar terms the average direct cost of research project grants has declined 13 percent in the past 15 years.

- The success rate for project grant applications filed with NIH during 1986 was 34 percent.

- During the past five years we have supported about 10,500 trainees and fellows per year. The yield of future NIH grant applicants from among research fellows with Ph.D. or M.D. degrees, or of trainees with Ph.D. degrees has been satisfactory, but the yield from among M.D.s has been low, although the situation has been improving somewhat.

- The NIH faces a serious problem in the funding of research training programs. Tuition costs are increasing rapidly in both the predoctoral and medical scientist training programs,

AND WITHOUT SUBSTANTIAL INCREASES IN THE APPROPRIATIONS FOR THESE ACTIVITIES, WE FACE A CHOICE BETWEEN CONTINUING TO PAY FULL TUITION COSTS OR MAINTAINING THE CURRENT NUMBER OF TRAINEES.

THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS

- ON JUNE 15 AND 16 THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH, WILL DEVOTE ITS 55TH MEETING TO DISCUSSIONS OF THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS, INCLUDING UNIVERSITIES, MEDICAL SCHOOLS AND INDEPENDENT BIOMEDICAL RESEARCH INSTITUTIONS. SPECIFIC ISSUES ASSOCIATED WITH THE SUPPORT OF BASIC BIOMEDICAL RESEARCH AND WITH CLINICAL RESEARCH WILL BE CONSIDERED.

USE OF ANIMALS AS SUBJECTS OF BIOMEDICAL RESEARCH

- THE SMALL SEGMENT OF SOCIETY OPPOSED TO THE USE OF ANIMALS IN RESEARCH HAS CONTINUED TO CLAMOR FOR HEADLINES AND TELEVISION TIME TO INFLUENCE THE PUBLIC AGAINST ESSENTIALLY ALL USES OF ANIMALS IN BIOMEDICAL RESEARCH. BREAK-INS, VANDALISM, MAJOR DESTRUCTION OF PROPERTY, AND THEFT OF ANIMALS HAS CONTINUED.

- ON APRIL 6, 1987 THE U.S. SUPREME COURT TOOK ACTION WHOSE EFFECT CONFIRMED A DECISION BY A LOWER COURT THAT ANIMAL RIGHTS GROUPS DO NOT HAVE STANDING IN COURT TO BRING SUIT ON

BEHALF OF ANIMAL SUBJECTS OF RESEARCH. THIS IMPORTANT DECISION REMOVES A THREAT OF WIDESPREAD AND PROTRACTED LITIGATION.

MORE ON AIDS BUDGETS AND ADMINISTRATIVE ACTIVITIES
(ADDITIONAL TO FAUCI PRESENTATION)

- THE PROMISE OF NEW APPROACHES TO DRUG DEVELOPMENT HAS LED NIH TOWARD A SPECIAL INITIATIVE TO DEVELOP TARGETED ANTIVIRAL COMPOUNDS, PARTICULARLY FOCUSED ON AIDS.

- WE HAVE DEVELOPED AN NIH PROGRAM TO STIMULATE BASIC RESEARCH AND MOBILIZE THE SCIENTIFIC RESOURCES AND CAPABILITIES THAT EXIST IN BOTH THE INTRAMURAL LABORATORIES OF THE NIH AND UNIVERSITIES AND INDUSTRIAL LABORATORIES ACROSS THE COUNTRY. TO IMPLEMENT THE INITIATIVE $10 MILLION WAS APPROPRIATED IN THE FY 1987 BUDGET AND A SIMILAR AMOUNT IS INCLUDED IN THE 1988 REQUEST.

- THE INTRAMURAL COMPONENT OF THE PROGRAM IS INTENDED TO MOBILIZE THE RESOURCE OF SCIENTIFIC TALENT FOUND IN THE VARIOUS LABORATORIES OF THE NIH TO BETTER FOCUS ON THE BIOLOGY AND FINE STRUCTURE OF VIRUSES AS WELL AS THE DEVELOPMENT OF SPECIFIC DRUGS THAT INHIBIT VIRAL ATTACHMENT, PENETRATION, REPLICATION, INTEGRATION AND EXPRESSION.

- An extramural counterpart will be established through the support of several multidisciplinary research groups that will also be centered around the theme of development of targeted antiviral drugs. These research groups will also provide training for graduate students.

- The NIAID/NCI National Cooperative Drug Discovery Groups for the Treatment of AIDS initiated in 1986 provides a broad-based program that incorporates a variety of approaches directed toward the discovery of more effective therapies for the treatment of AIDS.

- The NIH overall AIDS program includes a comprehensive array of activities involving grant support for research leading to candidate anti-HIV drugs, contract support for screening units to evaluate candidate drugs for <u>in vitro</u> anti-HIV activity, preclinical testing in animals, selection of drugs for further testing, and phase I and phase II clinical testing conducted in 19 AIDS Treatment Evaluation Units throughout the country.

- The FY 1987 budget for AIDS research by NIH is $252,483. The FY 1988 budget request is for $343,468.

MORE ON HUMAN GENOME

(ADDITIONAL TO PRESENTATION BY DR. KIRSCHSTEIN)

- A SUBCOMMITTEE ON THE HUMAN GENOME HAS BEEN ESTABLISHED UNDER THE WORKING GROUP ON BIOLOGY OF THE WHITE HOUSE DOMESTIC COUNCIL. THE SUBCOMMITTEE INCLUDES REPRESENTATION FROM THE DEPARTMENT OF ENERGY, THE NATIONAL SCIENCE FOUNDATION, THE FOOD AND DRUG ADMINISTRATION, THE ENVIRONMENTAL PROTECTION AGENCY, THE DEPARTMENT OF AGRICULTURE, AND IS CHAIRED BY THE NATIONAL INSTITUTES OF HEALTH. THE FIRST MEETING OF THE SUBCOMMITTEE WAS HELD MAY 8.

BIG SCIENCE

- THE ISSUES INVOLVED IN SEQUENCING THE HUMAN GENOME AND THE DECISION TO ESTABLISH A LIMITED NUMBER OF STRUCTURAL BIOLOGY CENTERS FOR EXPLORATION OF THE AIDS VIRUS AND DEVELOPMENT OF THE ANTIVIRAL AGENTS HAVE GENERATED A HEIGHTENED INTEREST IN THE QUESTION OF "BIG SCIENCE" IN BIOLOGY. THE NIH HAS TAKEN A FEW STEPS IN THAT DIRECTION WITH PROGRAM PROJECT GRANTS AND CENTER AWARDS BUT THE DOMINANT MECHANISM REMAINS THE INVESTIGATOR-INITIATED RESEARCH PROJECT GRANT.

- THE HOWARD HUGHES INSTITUTE IS BEGINNING TO FUND LARGE UNITS WITH SPECIFIC PROGRAM ORIENTATION IN SOME 20 OR MORE LEADING INSTITUTIONS, WITH GENEROUS SUPPORT AND MAXIMUM FLEXIBILITY.

- THE ROLE OF "BIG SCIENCE" IN BIOLOGICAL RESEARCH HAS NOT BEEN ADDRESSED AS A PUBLIC POLICY ISSUE. THE TOPIC IS TO RECEIVE THE ATTENTION OF A STUDY TO BE CONDUCTED BY THE INSTITUTE OF MEDICINE OF THE NATIONAL ACADEMY OF SCIENCES, AND PARTLY FUNDED BY THE NIH.

DRAFT SW

OPENING REMARKS*

BY

JAMES B. WYNGAARDEN, M.D.**

I AM DELIGHTED TO HAVE THE PRIVILEGE OF ADDING MY WORD OF WELCOME TO EACH OF YOU AS YOU BEGIN THE 1987 ANNUAL MEETING OF THE AMERICAN RHEUMATISM ASSOCIATION. FOR A PARTICULAR INSTITUTIONAL REASON MY NIH COLLEAGUES AND I ARE ESPECIALLY PLEASED THAT YOU ARE MEETING IN WASHINGTON IN 1987. FOR THIS IS THE CENTENNIAL YEAR OF THE NATIONAL INSTITUTES OF HEALTH, AND WE CONSIDER YOUR MEETING FORTUITOUSLY TO BE A PART OF THE CELEBRATION OF OUR 100TH BIRTHDAY.

BEGINNING WITH AN OFFICIAL OPENING CEREMONY IN MID-OCTOBER 1986, IT HAS BEEN MY PLEASANT DUTY TO PARTICIPATE IN QUITE A VARIETY OF CENTENNIAL-RELATED EVENTS IN MANY DIFFERENT PARTS OF THE UNITED STATES. MANY MORE ARE SCHEDULED BOTH HERE AND ABROAD. WE DECIDED TO DEVOTE SUBSTANTIAL EFFORT TO THE CENTENNIAL BECAUSE WE FEEL THAT THE OCCASION PROVIDES US WITH AN OPPORTUNITY TO ACQUAINT THE AMERICAN PEOPLE WITH THE LONG-TERM NECESSITY FOR BIOMEDICAL RESEARCH, TO POINT OUT THE HEALTH BENEFITS THAT HAVE BEEN DERIVED FROM MEDICAL SCIENCE, AND TO ADDRESS PUBLICLY TOMORROW'S CHALLENGES. THE SECOND MAJOR PURPOSE OF OUR CENTENNIAL ACTIVITIES IS TO BRING TO THE

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*PRESENTED AT THE AMERICAN RHEUMATISM ASSOCIATION ANNUAL MEETING, WASHINGTON, D.C., JUNE 9, 1987

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

ATTENTION OF YOUNG PEOPLE THE OPPORTUNITIES FOR THEM IN BIOMEDICAL RESEARCH--THE EXCITEMENT--THE REWARDS--AND THE POTENTIAL SERVICE TO THE GENERAL GOOD THROUGH RESEARCH CAREERS.

THESE MESSAGES--THE VITAL ROLE OF BIOMEDICAL RESEARCH, AND THE NEED FOR CONTINUOUS REPLENISHMENT OF THE CADRE OF YOUNG SCIENTISTS--ARE IMPORTANT TO ALL SECTORS OF THE HEALTH PROFESSIONS, AS WELL AS TO THE PUBLIC AT LARGE. THUS IT IS OUR VIEW OF THE NIH CENTENNIAL THAT IT PROVIDES WHAT IS LITERALLY A ONCE-IN-A-LIFETIME PLATFORM OF OPPORTUNITY FOR SPEAKING OUT TO THE AMERICAN PEOPLE.

IT IS MORE THAN A TIME FOR NOSTALGIA, BUT IN THE COURSE OF REVIEWING THE HISTORY OF MEDICINE FOR THE PAST CENTURY, ONE ENCOUNTERS MANY INTERESTING AND INSPIRING CHAPTERS. RATHER THAN RECITING ANY DETAILS OF THAT HISTORY JUST NOW, I WILL MENTION THAT NEXT FALL--AT TIMES YET TO BE ANNOUNCED--WE EXPECT A FOUR-PART SERIES OF ONE-HOUR TELEVISION PROGRAMS ON PBS TO TELL THE STORY OF MEDICINE AND RESEARCH FOR THE PAST HUNDRED YEARS AND OF THE NIH ROLE IN WHAT WE HAVE CALLED "A CENTURY OF SCIENCE FOR HEALTH." THESE PROGRAMS, AS WELL AS OTHER OF OUR CENTENNIAL OBSERVANCES, ARE FUNDED BY GENEROUS CONTRIBUTIONS OF 14 LEADING PHARMACEUTICAL COMPANIES AND THE HOWARD HUGHES MEDICAL INSTITUTE.

I MUST MENTION ONE SPECIFIC EVENT, SO RECENT THAT IT DOES NOT QUALIFY AS HISTORY. I AM SPEAKING OF THE CREATION OF THE NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES AS THE TWELFTH OF THE MAJOR CONSTITUENT UNITS OF THE NIH. IN THE WORDS OF CONGRESSMAN CLAUDE PEPPER, LONGTIME ADVOCATE OF THE INSTITUTE, ITS PURPOSE IS TO PROVIDE A "SHARP NEW FOCUS" ON ARTHRITIS RESEARCH. WITH THE APPROVAL OF P.L. 99-158 IN NOVEMBER 20, 1985, THE NEW INSTITUTE CAME INTO BEING. IN APRIL LAST YEAR DR. LAWRENCE SHULMAN WAS NAMED ACTING DIRECTOR, AND ON JANUARY 16, 1987 HE WAS APPOINTED DIRECTOR. DR. SHULMAN, AN INTERNATIONALLY KNOWN RHEUMATOLOGIST, CAME TO NIH IN 1976 FROM THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE TO DEVELOP AND CARRY OUT THE SEVERAL PROGRAMS THAT HAD BEEN RECOMMENDED IN THE "ARTHRITIS PLAN" THAT HAD BEEN CALLED FOR BY THE CONGRESS AND WAS OFFICIALLY SUBMITTED THAT YEAR. HE BRINGS TO THE POSITION OF THE INSTITUTE'S FIRST DIRECTOR AN INTIMATE KNOWLEDGE OF THE FOUNDATION OF PUBLIC, PROFESSIONAL, SCIENTIFIC AND CONGRESSIONAL INTEREST ON WHICH THE NEW ENTITY WAS BUILT.

THUS, THE NIH IS CELEBRATING THE NEW AS WELL AS THE OLD. REFERRING TO THE NEW INSTITUTE, I HAVE SPOKEN OF THIS AS THE TIME OF THE "CENTENARIAN AND THE YEARLING."

IT IS WITH REAL PLEASURE THAT ONCE AGAIN I EXTEND TO YOU THE WARMEST WELCOME.

DRAFT SW

KEYNOTE ADDRESS*

BY

JAMES B. WYNGAARDEN, M.D.**

YOUR INVITATION TO PARTICIPATE IN THIS PLEASANT OCCASION HAS GIVEN ME A WELCOME OPPORTUNITY TO EXPRESS PERSONALLY AND ON BEHALF OF MY NIH COLLEAGUES OUR APPRECIATION TO SOME OF OUR VALUED NEIGHBORS FOR CONSISTENT INTEREST IN AND SUPPORT OF OUR INSTITUTION. OUR THANKS ARE DUE ESPECIALLY TO THE MEMBERS OF THE BIOMEDICAL RESEARCH COMMUNITY WHO ARE REPRESENTED SO APPROPRIATELY BY TONIGHT'S HONOREES.

WE ARE NOW BEYOND THE HALFWAY POINT OF A YEAR-LONG OBSERVANCE OF THE CENTENNIAL ANNIVERSARY OF THE NATIONAL INSTITUTES OF HEALTH. AT A VARIETY OF EVENTS HELD IN MANY DIFFERENT PARTS OF THE UNITED STATES, WE HAVE EMPHASIZED THE ACCOMPLISHMENTS OF "PARTNERS IN DISCOVERY"--THE INSTITUTIONS IN GOVERNMENT, ACADEMIA AND INDUSTRY THAT HAVE WORKED TOGETHER IN THE CONDUCT OF BIOMEDICAL RESEARCH IN WHAT HAS TRULY BEEN A "CENTURY OF SCIENCE FOR HEALTH." THE SIGNIFICANT PROGRESS IN BIOMEDICAL RESEARCH OVER THE PAST 100 YEARS HAS, IN FACT, BEEN ACHIEVED IN SUBSTANTIAL MEASURE THROUGH A UNIQUE PARTNERSHIP AMONG THE U.S. GOVERNMENT, ACADEMIA AND INDUSTRY. WORKING INDEPENDENTLY OR TOGETHER, THE PUBLIC AND PRIVATE SECTORS

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*PRESENTED AT THE B'NAI-B'RITH ANTI-DEFAMATION LEAGUE AWARDS DINNER, ROCKVILLE, MARYLAND, JUNE 16, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

HAVE MADE DISCOVERIES THAT HAVE DRAMATICALLY IMPROVED THE STATE OF AMERICAN HEALTH.

NEW KNOWLEDGE OF BIOLOGICAL PROCESSES IS THE FOUNDATION OF ALL PROGRESS IN THE HEALTH SCIENCES. YET, MEDICAL RESEARCH THAT LEADS TO PROGRESS TAKES YEARS OF PATIENT, OFTEN FRUSTRATING AND COMPLEX EXPERIMENTATION BY MANY DIFFERENT TEAMS THROUGHOUT THE SCIENTIFIC COMMUNITY. EACH PARTNER BUILDS ON THE KNOWLEDGE ACQUIRED AND THE CONCEPTS TESTED BY THE OTHERS. IN THIS WAY, OUR GOVERNMENT, UNIVERSITY AND INDUSTRIAL LABORATORIES HAVE MADE THE UNITED STATES THE WORLD LEADER IN BIOMEDICAL RESEARCH. IT MUST ALSO BE NOTED THAT VOLUNTARY HEALTH ORGANIZATIONS PLAY AN IMPORTANT PART IN THIS UNIQUE PARTNERSHIP. THEIR SUPPORT OF BIOMEDICAL RESEARCH AND THEIR PUBLIC EDUCATION PROGRAMS ARE INVALUABLE IN INCREASING PUBLIC AWARENESS OF THE IMPORTANCE OF BIOMEDICAL RESEARCH AND IN STIMULATING NEW RESEARCH ENDEAVORS.

IN EXPRESSING SOME OF THE THINGS I WISH TO SAY ABOUT THE PARTNERSHIP FOR DISCOVERY, I WILL DO SO IN THE CONTEXT OF THE HISTORICAL BACKGROUND OF THE NATIONAL INSTITUTES OF HEALTH. LET ME TELL YOU BRIEFLY ABOUT THE NIH AND THE MECHANISMS IT EMPLOYS FOR THE CONDUCT AND SUPPORT OF BIOMEDICAL RESEARCH. I WILL BE DESCRIBING SOME OF THE LONG-STANDING AS WELL AS DEVELOPING LINKAGES BETWEEN OUR PROGRAMS AND THE RESEARCH ENDEAVORS OF OUR PARTNERS IN ACADEMIA AND INDUSTRY.

As would be expected, the National Institutes of Health has undergone many changes during the past century, some of them extensive. For the first half of its history the NIH was, in essence, a small Federal laboratory carrying out important research within its own confines, but its resources were such that at a given time only a very limited number of studies could be conducted.

In its 50th year, 1936, the total of all employees assigned to the NIH was less than 200 and of this number about 90 were scientific or technical personnel.

At this time there are about 13,000 NIH personnel, some 3,000 with doctoral degrees. Of this number more than 1,100 are intramural scientists conducting laboratory and clinical research in NIH facilities. In addition, at any given time some 900 postdoctoral M.D. and Ph.D. trainees are participating in our regular on-campus training programs. The number of intramural scientists is further augmented by an average of 1,500 visiting and guest scientists from more than 70 countries.

From a one-room laboratory in the attic of the Marine Hospital facility on Staten Island, where the NIH began in 1887, the institution has grown to a facility with more than 40 buildings, including the 500-bed Clinical Center, on the 300-acre main campus in Bethesda; an extensive installation

AT THE RESEARCH TRIANGLE IN NORTH CAROLINA, WHERE THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH IS LOCATED; THE ROCKY MOUNTAIN LABORATORY IN MONTANA; AND A FEW SMALL INSTALLATIONS ELSEWHERE.

BUT THE PROGRAMS OF THE NATIONAL INSTITUTES OF HEALTH CARRIED OUT IN OUR OWN FACILITIES ARE NOW ONLY A MINOR PART OF THE WHOLE.

THE FIRST SIGNIFICANT GROWTH OF THE INTRAMURAL PROGRAMS PARALLELED THE NATIONAL DEFENSE BUILDUP PRIOR TO WORLD WAR II, BUT THIS GROWTH WAS ECLIPSED SHORTLY BY THE MAJOR CHANGES THAT TOOK PLACE IN THE AGENCY THROUGH THE ADDITION OF A NEW DIMENSION--OUR EXTRAMURAL PROGRAMS.

THE CHANGE TOOK PLACE IN THE ADJUSTMENT PERIOD AT THE END OF THE WAR, WHEN THE POLICY OF THE FEDERAL GOVERNMENT WITH REGARD TO THE CONDUCT OF RESEARCH WAS REVISED DRASTICALLY. AT THE TIME THE WARTIME OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT (OSRD) WENT OUT OF BUSINESS DECEMBER 31, 1945, SOME 250 HEALTH-RELATED RESEARCH PROJECTS WERE BEING FUNDED AT UNIVERSITIES, HOSPITALS, AND OTHER LABORATORIES. THESE UNFINISHED PROJECTS WERE TURNED OVER TO THE NIH FOR ADMINISTRATION. IT IS SIGNIFICANT THAT THE RESEARCH PROJECTS WERE NOT CANCELLED, AND THAT INSTEAD A MECHANISM WAS PUT IN PLACE FOR CONTINUING TO AWARD MORE SUCH GRANTS AND CONTRACTS.

RELIANCE ON NON-FEDERAL LABORATORIES FOR THE CONDUCT OF FEDERALLY-SUPPORTED RESEARCH IN PEACETIME WAS A MAJOR DEPARTURE FROM PAST SCIENCE POLICIES. THIS NEW POLICY WAS RESPONSIBLE FOR THE ESTABLISHMENT OF THE MODERN NIH.

BY FAR, THE LARGEST PART OF NIH RESEARCH TODAY TAKES PLACE IN SOME 1600 UNIVERSITIES, MEDICAL SCHOOLS, HOSPITALS, INDEPENDENT AND INDUSTRIAL LABORATORIES. LAST YEAR THE NIH FUNDED MORE THAN 28,000 RESEARCH AND RESEARCH TRAINING PROJECTS INVOLVING APPROXIMATELY 50,000 NON-FEDERAL SCIENTISTS. ALMOST 90 PERCENT OF THE AGENCY'S BUDGET OF MORE THAN $6 BILLION IS DEVOTED TO SUCH AWARDS AND THE RELATED ADMINISTRATIVE COSTS.

THE KEY MECHANISM USED BY NIH FOR DEPLOYMENT OF THE SCIENTIFIC COMMUNITY'S CREATIVE ENERGIES IN BIOMEDICAL RESEARCH IS THE INVESTIGATOR-INITIATED PROJECT GRANT. IT IS USED FOR SUPPORTING THE MAJORITY OF OUR EXTRAMURAL RESEARCH. WELL OVER HALF OF OUR TOTAL BUDGET IS ALLOCATED TO SUCH PROJECTS FOR THE CONDUCT OF RESEARCH BY NON-FEDERAL INVESTIGATORS. SUCH INVESTIGATOR-INITIATED RESEARCH DRAWS UPON THE EXPERTISE AND INTUITION OF PRACTICALLY THE ENTIRE AMERICAN SCIENTIFIC COMMUNITY. IN RECENT YEARS THE NUMBER AND QUALITY OF RESEARCH PROPOSALS HAS INCREASED STEADILY, SO THAT EVEN THOUGH OUR APPROPRIATIONS HAVE INCREASED FROM YEAR TO YEAR, WE ARE ABLE CURRENTLY TO FUND ONLY JUST OVER A THIRD OF THE MERITORIOUS GRANT PROPOSALS WE RECEIVE EACH YEAR.

WITH THE RAPID EXPANSION OF SUPPORT FOR THE EXTRAMURAL PROGRAM, THE NUMBER OF APPLICATIONS FOR SUPPORT GREW EVEN MORE RAPIDLY. WHEN THE EXTRAMURAL PROGRAM WAS FIRST ESTABLISHED IT WAS RECOGNIZED THAT IT WOULD BE NECESSARY TO DEVISE A SENSITIVE AND EFFECTIVE MECHANISM FOR SELECTING THE MOST MERITORIOUS PROJECTS FROM THE PROPOSALS FOR GRANTS AND CONTRACTS. THE SYSTEM DEVELOPED BY THE NIH FOR THIS CRITICALLY IMPORTANT FUNCTION HAS SERVED WELL THE INTERESTS OF SCIENCE AND OUR HEALTH-RELATED MISSION. THE NIH PEER REVIEW SYSTEM HAS BEEN EMULATED IN A NUMBER OF OTHER COUNTRIES.

THE AVERAGE TERM OF RESEARCH PROJECT GRANTS IS NOW 3.7 YEARS, AND THE AVERAGE TOTAL COST PER GRANT REACHED $152,000 IN 1986.

THE OVERALL BUDGET OF THE NATIONAL INSTITUTES OF HEALTH FOR FISCAL YEAR 1988 IS NOW BEFORE THE CONGRESS, AND AT THIS POINT WE ARE NOT DISCOURAGED BUT ARE NOT SURE HOW ENCOURAGED TO BE. I WILL COMMENT, HOWEVER, THAT THE 1987 BUDGET OF THE NIH WAS INCREASED OVERALL ABOUT 17 PERCENT OVER THE FY 1986 BUDGET. WE RECOGNIZE THAT AN INCREASE OF THIS MAGNITUDE DURING A TIME OF BUDGET RESTRAINT IS AN INDICATION OF THE LEVEL OF CONFIDENCE THAT EXISTS IN THIS COUNTRY AS TO THE LONG-TERM VALUE OF BIOMEDICAL RESEARCH. AS IN PREVIOUS YEARS, THIS CONTINUED GENEROUS SUPPORT APPEARS TO RESULT FROM AN APPRECIATION OF THE OVERARCHING IMPORTANCE OF RESEARCH

THAT MAY LEAD TO THE DEVELOPMENT OF NEW MEANS FOR THE PREVENTION, TREATMENT OR CURE OF DISEASE AND DISABILITY.

THE INCREASE LAST YEAR WAS LARGER THAN THE GAINS IN MOST YEARS FOR THE PAST TWO DECADES, BUT OVERALL THE GROWTH HAS BEEN CONTINUOUS AND SUBSTANTIAL. DURING THIS SAME PERIOD INDUSTRY HAS SUPPLIED AN INCREASING SHARE OF NATIONAL FUNDING FOR HEALTH RESEARCH AND DEVELOPMENT. TWENTY YEARS AGO INDUSTRY AS A WHOLE WAS RESPONSIBLE FOR 24 PERCENT OF HEALTH RESEARCH AND DEVELOPMENT; IN 1970 IT HAD RISEN TO 28 PERCENT; BY 1980 IT WAS 31; AND BY 1986 INDUSTRY'S SHARE HAD INCREASED TO 39 PERCENT. AS A FOOTNOTE I SHOULD MENTION THAT IN THE ERA OF THE "MODERN" NIH ITS CONTRIBUTION TO NATIONAL HEALTH RESEARCH AND DEVELOPMENT EACH YEAR EXCEEDED THE TOTAL INVESTED BY ALL OF INDUSTRY UNTIL 1983. IN 1986 THE NIH SHARE WAS ABOUT 35 PERCENT AS COMPARED WITH INDUSTRY'S 39.

RECENT YEARS HAVE ALSO SEEN THE ESTABLISHMENT OF NEW TIES BETWEEN INDUSTRIAL ORGANIZATIONS AND SOME OF THE NATION'S LEADING ACADEMIC ORGANIZATIONS FOR THE PURPOSE OF EXPANDING BIOMEDICAL RESEARCH ACTIVITIES. THE NIH HAS AN OBVIOUS INTEREST IN SUCH NEW PARTNERSHIPS INVOLVING THE INSTITUTIONS THAT FOR YEARS HAVE BEEN CLOSELY LINKED WITH US THROUGH OUR EXTRAMURAL PROGRAMS. WE HAVE NOT INTERPOSED OURSELVES IN THE NEW ARRANGEMENTS AND HAVE NO INTENTION OF DOING SO.

Important links between the NIH and industry were established more than 30 years ago with the development of the NIH patent policy that became the model for the Stevenson Wydler Technology Innovation Act of 1980.

At different levels in the NIH programs there have been increasing interactions with industry. Provisions have been made to permit NIH scientists to lecture at and consult with industrial organizations, and guest investigators from industry may now be accommodated within the NIH intramural laboratories. We are now jointly sponsoring conferences for the direct exchange of scientific information between our scientists and their industrial counterparts.

Recently the administration and the Congress have become interested in the direct economic consequences of the national investment that has been responsible for the emergence of biotechnology.

Biotechnology is not a new phenomenon of the 1980s--in fact, it has a long history, certainly as long as that of the NIH. A century ago, Louis Pasteur was engaged in research that changed, profoundly, the course of the biosciences and medicine. We sometimes forget how industry was also a direct object and beneficiary of a substantial portion of Pasteur's work. Perhaps the simplest way to describe this relationship is to cite the entry on Pasteur in the Encyclopedia Britannica,

WHERE HIS ACCOMPLISHMENTS ARE SUMMARIZED IN THE FOLLOWING SENTENCE. "PASTEUR PROVED THAT MICROORGANISMS CAUSE FERMENTATION AND DISEASE; HE ORIGINATED AND WAS THE FIRST TO USE VACCINES FOR RABIES, ANTHRAX, AND CHICKEN CHOLERA; HE SAVED THE WINE, BEER AND SILK INDUSTRIES OF FRANCE AND ELSEWHERE; HE PERFORMED IMPORTANT PIONEER WORK IN STEREOCHEMISTRY; (AND) HE ORIGINATED PASTEURIZATION."

A STRIKINGLY SIMILAR MODERN VERSION OF THIS CATALOG OF ACCOMPLISHMENTS IN BIOTECHNOLOGY COULD BE WRITTEN ABOUT THE DIRECT AND INDIRECT BENEFITS OF BASIC RESEARCH ON MOLECULAR BIOLOGY.

BIOTECHNOLOGY HAS HAD AN IMPACT ON THE CONDUCT OF BASIC BIOMEDICAL RESEARCH COMPARABLE PERHAPS TO THAT OF THE COMPUTER ON INFORMATION PROCESSING. BIOTECHNOLOGY HAS MOVED US AHEAD BY LEAPS AND BOUNDS IN UNDERSTANDING CANCER, GENETIC DEFECTS, ORGAN TRANSPLANTATION BIOLOGY, CLINICAL IMMUNOLOGY AND ALLERGIC RESPONSE, AND BONE DEVELOPMENT AND REPAIR, JUST TO NAME A FEW AREAS.

BIOTECHNOLOGY HAS CREATED AN UNPRECEDENTED SET OF OPPORTUNITIES, ISSUES AND CONCERNS IN WHICH THE NATIONAL INSTITUTES OF HEALTH HAS MORE THAN A CASUAL INTEREST. THIS IS BECAUSE THE BODY OF KNOWLEDGE ON WHICH THE BIOTECHNOLOGY INDUSTRY IS BASED WAS LARGELY THE RESULT OF SUSTAINED SUPPORT

FOR BASIC RESEARCH IN MOLECULAR BIOLOGY AND IMMUNOLOGY PROVIDED BY THE NIH OVER THE PAST FEW DECADES.

THE NIH CONTINUES TO MAKE A MAJOR COMMITMENT TO THE FUTURE OF BIOTECHNOLOGY. THE PROPORTION OF THE NIH BUDGET DEVOTED TO BIOTECHNOLOGY HAS REMAINED ESSENTIALLY CONSTANT FOR THE PAST FIVE YEARS, WITH ABOUT 11 PERCENT DEVOTED TO DIRECTLY RELATED RESEARCH, AND ABOUT 25 PERCENT DEVOTED TO UNDERLYING BASIC RESEARCH AND RESEARCH TRAINING.

IF 20 YEARS AGO THE NIH DIRECTOR HAD TALKED OF THE NIH ROLE WITH RESPECT TO BIOTECHNOLOGY AS I HAVE DONE, IT IS LIKELY THAT THE DISCUSSION WOULD HAVE BEEN CONSIDERED INAPPROPRIATE, OR AT BEST ENTIRELY SPECULATIVE. YET, AT THAT TIME MUCH OF THE SCIENCE BASE ON WHICH THE NEW TECHNOLOGY DEPENDS HAD BEEN DISCOVERED OR WAS BEING ELUCIDATED IN THE COURSE OF BASIC RESEARCH. ROBERT OPPENHEIMER CHARACTERIZED THE MOTIVATION FOR SUCH RESEARCH IN AN ARRESTING SENTENCE. "IT IS A PROFOUND AND NECESSARY TRUTH," HE SAID, "THAT THE DEEP THINGS IN SCIENCE ARE NOT FOUND BECAUSE THEY ARE USEFUL; THEY ARE FOUND BECAUSE IT WAS POSSIBLE TO FIND THEM."

ABOUT TWO YEARS AGO, AT MY SUGGESTION, THE NIH'S PRINCIPAL ADVISORY COMMITTEE SET ASIDE A TWO-DAY MEETING TO DISCUSS IN A PUBLIC FORUM THE PROPER ROLE FOR THE NIH IN THE ARENA OF BIOTECHNOLOGY. THE CONSENSUS WAS THAT WE SHOULD CONTINUE TO DO WHAT WE DO BEST, THAT IS, TO CONTINUE TO

CONDUCT AND SUPPORT RESEARCH AND RESEARCH TRAINING WITH CONTINUED EMPHASIS ON BASIC RESEARCH.

THAT CONCLUSION WAS SIMILAR TO ONE REACHED AT ABOUT THE SAME TIME BY THE PRESIDENT'S SCIENCE ADVISOR, GEORGE KEYWORTH, FOLLOWING A REVIEW OF FEDERAL SCIENCE POLICY. HE REPORTED, "PERHAPS THE MOST IMPORTANT ELEMENT OF POLICY THAT EMERGED FROM RECENT REASSESSMENTS WAS A RENEWED--AND CONSIDERABLY STRENGTHENED FEDERAL SUPPORT FOR BASIC RESEARCH. ....QUITE SIMPLY, BASIC RESEARCH IS A VITAL UNDERPINNING FOR OUR NATIONAL WELLBEING."

THE FULL SPECTRUM OF THE BIOLOGICAL SCIENCES IN THE SERVICE OF MANKIND, HOWEVER, EXTENDS FROM THE MOST BASIC MOLECULAR BIOLOGY TO THE APPLICATION OF THE FRUITS OF RESEARCH TO THE TREATMENT OF PREVENTION OF DISEASE. THE HONORS BEING AWARDED TONIGHT ARE FOR CONTRIBUTIONS ACROSS THAT SPECTRUM.

AN INSCRIPTION ON THE DOME OF THE GREAT HALL OF THE NATIONAL ACADEMY OF SCIENCES COULD WELL BE A TOAST FOR THIS OCCASION. I WILL CONCLUDE WITH ITS WORDS, "....TO SCIENCE: PILOT OF INDUSTRY, CONQUEROR OF DISEASE, MULTIPLIER OF THE HARVEST, EXPLORER OF THE UNIVERSE, REVEALER OF NATURE'S LAW AND ETERNAL GUIDE TO TRUTH."

DRAFT S.

REMARKS*

BY

JAMES B. WYNGAARDEN, M.D.**

IF I WERE TO ASK INDIVIDUALLY THE MEMBERS OF THIS AUDIENCE SUCH A QUESTION AS "WHAT ARE THE THINGS YOU ESPECIALLY LIKE ABOUT NIH?", IT IS PROBABLE THAT I WOULD BE GIVEN MANY DIFFERENT ANSWERS. SOME OF YOU WOULD SPEAK OF THE SATISFACTIONS FROM SERVICE TO HUMANITY THROUGH WORKING TO IMPROVE HEALTH; SOME WOULD MENTION THE PLEASANT SURROUNDINGS--THE BEAUTY OF OUR MAGNIFICENT CAMPUS; AND SOME WOULD MENTION THE CHALLENGE AND EXCITEMENT OF RESEARCH. IT IS MY GUESS, HOWEVER, THAT THE MOST FREQUENT RESPONSE WOULD BE SOMETHING SIMILAR TO "I ESPECIALLY LIKE WORKING AT NIH BECAUSE OF THE PEOPLE WHO ARE HERE--MY CO-WORKERS."

THIS IS INDEED A REMARKABLE COMMUNITY OF TALENTED AND DEDICATED PERSONS. THERE IS GREAT DIVERSITY AMONG THE SCIENTISTS, TECHNICIANS, ADMINISTRATORS, AND THE SKILLED PERSONNEL WHO PERFORM THE ESSENTIAL TASKS THAT MUST BE DONE IF THE NIH IS TO PERFORM ITS MISSION. WITH ALL THIS DIVERSITY THERE IS A COMMON DEVOTION TO EXCELLENCE. AND THAT IS WHAT THIS HONOR AWARDS CEREMONY IS ALL ABOUT.

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*PRESENTED AT THE NIH HONOR AWARDS CEREMONY, MASUR AUDITORIUM, JUNE 22, 1987.

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As in previous years I have been struck by the range of occupations represented by the honorees today. Simply reading through the list of awardees and their citations is to learn something new about the scope of our activities and the wealth of human resources that NIH enjoys.

We are now beyond the mid point of the year-long observance of the NIH centennial. It has been a time for reviewing chapters of our history and for recalling the accomplishments of many of the individuals whose careers were invested here.

This is a particularly appropriate occasion for remembering some of our predecessors whose influence persists in the NIH tradition. Permit me to present some historical capsules.

The first one should be dated about 1885, when our founding director, Dr. Joseph Kinyoun, was selected by public health authorities to go to Europe, to study with Pasteur and Koch in the hope that he would learn how to ward off the importation of a new wave of cholera into the United States. Upon his return, young Dr. Kinyoun set up a bacteriological laboratory in the Marine Hospital on Staten Island in 1887. The NIH is the direct descendant of that laboratory.

By 1909 the Hygienic Laboratory had been in Washington for 18 years and was in its own quarters at 25th and E Streets where it stayed until 1938. The staff had reached a total of

53, JUST 9 MORE THAN THE NUMBER BEING HONORED TODAY. AMONG THAT NUMBER WERE SOME HEROES OF MEDICINE, SUCH AS DR. HOWARD TAYLOR RICKETTS, WHOSE WORK ON ROCKY MOUNTAIN SPOTTED FEVER PROVIDED THE KEY FOR FINDING THE CAUSE OF EPIDEMIC TYPHUS. RICKETTS DIED OF TYPHUS IN 1910, A VICTIM OF THE ORGANISM HE HAD EARLIER DESCRIBED AND THAT SUBSEQUENTLY WAS NAMED FOR HIM--THE RICKETTSIA.

IN 1914 ANOTHER REMARKABLE MEMBER OF THE STAFF, DR. JOSEPH GOLDBERGER, WAS PLACED IN CHARGE OF THE PUBLIC HEALTH SERVICE INVESTIGATION OF PELLAGRA. PELLAGRA, A SERIOUS PROBLEM IN THE SOUTH, WAS THOUGHT BY MOST MEDICAL AUTHORITIES TO BE AN INFECTIOUS DISEASE. FROM HIS OWN INVESTIGATION, GOLDBERGER BECAME CONVINCED THAT PELLAGRA WAS CAUSED BY POOR NUTRITION, AND FOR THE REMAINING 15 YEARS OF HIS LIFE MAINTAINED THAT POSITION AGAINST THE WEIGHT OF MEDICAL OPINION.

AT ONE POINT, TO PROVE THAT NO INFECTIOUS ORGANISM WAS INVOLVED, GOLDBERGER AND ONE OF HIS CO-WORKERS INJECTED EACH OTHER WITH BLOOD FROM A PELLAGRA PATIENT. LATER, GOLDBERGER AND FOUR OF HIS ASSOCIATES SWALLOWED CAPSULES CONTAINING PATIENTS' WASTES AND SKIN SCRAPINGS, AND GOLDBERGER INJECTED BLOOD FROM A PELLAGROUS WOMAN INTO HIS WIFE, MARY. NONE CONTRACTED THE DISEASE, ALTHOUGH IT IS NOT RECORDED WHAT ADVERSE SIDE EFFECTS THEY MAY HAVE EXPERIENCED. (NEEDLESS TO SAY, THE OFFICE FOR PROTECTION FROM RESEARCH RISKS DID NOT APPROVE THE EXPERIMENTS.)

IT WAS GOLDBERGER'S INSIGHT AND PERSISTENCE IN IT THAT CONQUERED PELLAGRA.

IN 1929 AT THE CLOSE OF THE YEAR AN OUTBREAK OF PSITTACOSIS OCCURRED SIMULTANEOUSLY IN EUROPE, NORTH AND SOUTH AMERICA. THE HYGIENIC LABORATORY WAS GIVEN THE TASK OF STUDYING THE DISEASE THAT HAD STIRRED FEARS OF AN EPIDEMIC. TWO LABORATORY ASSISTANTS, HENRY ANDERSON AND A "MRS. CARLIN," CONTRACTED THE DISEASE AND DIED. MANY LABORATORY WORKERS, AS WELL AS LEADING INVESTIGATORS, BECAME SERIOUSLY ILL WITH THE HIGHLY INFECTIOUS DISEASE. LABORATORY PERSONNEL WHO MERELY PASSED THE CLOSED DOORS OF THE ANIMAL ROOMS CAME DOWN WITH IT. FINALLY DIRECTOR GEORGE W. MCCOY DECREED THAT THE LABORATORY BUILDINGS MUST BE CLOSED AND THE PREMISES FUMIGATED. RISKING INFECTION WITH THE SERIOUS DISEASE, DR. MCCOY WENT ALONE INTO THE BASEMENT ROOMS WHERE EXPERIMENTAL ANIMALS WERE KEPT AND PERSONALLY CHLOROFORMED THEM.

THE WORK OF THE HYGIENIC LABORATORY HAD IDENTIFIED THE CAUSE AND MEANS OF TRANSMISSION OF THE DISEASE SO THAT ITS MENACE WAS MITIGATED. PSITTACOSIS FINALLY YIELDED TO ANTIBIOTICS.

A MOMENT AGO I TOLD HOW DEEPENING CONCERN ABOUT IMPORTING CHOLERA INTO THIS COUNTRY HAD PROVIDED THE IMPETUS FOR SELECTING DR. KINYOUN FOR ADVANCED TRAINING AND SUBSEQUENTLY THE ESTABLISHMENT OF THE LABORATORY OF HYGIENE. IN 1887 AND 1888

DR. KINYOUN WAS SUCCESSFUL IN ISOLATING VIBRIO CHOLERA, BUT STRICT QUARANTINE WAS CREDITED WITH PREVENTING THE THREATENED EPIDEMIC. PROGRESS IN UNDERSTANDING CHOLERA WAS PAINFULLY SLOW. THE TOXIN WAS NOT FOUND UNTIL 1959. DURING THE INTERIM THERE WERE MANY DIVERSIONS THAT OBSCURED THE DISCUSSIONS ON THE PATHOGENESIS OF CHOLERA AND THE ROLE OF THE TOXIN. A FRIEND OF MINE AND MANY IN THIS AUDIENCE, DR. ROBERT GORDON, WHILE A JUNIOR SCIENTIST HERE IN THE EARLY 1950S PARTICIPATED IN RESEARCH THAT CLEARED AWAY SOME OF THE CONFUSION ABOUT CHOLERA BY DECISIVELY PUTTING TO REST ONE OF THE HYPOTHESES THAT HAD STOOD IN THE WAY OF UNDERSTANDING THE DISEASE. DURING A PRODUCTIVE THREE-YEAR ASSIGNMENT IN DACCA AS CHIEF OF CLINICAL RESEARCH AT THE SEATO CHOLERA RESEARCH LABORATORY, DR. GORDON AND HIS CO-WORKERS DEVELOPED A THERAPEUTIC REGIMEN THAT NOT ONLY WAS HIGHLY EFFECTIVE IN PROMOTING RECOVERY OF CHOLERA PATIENTS BUT ALSO SHORTENED THE COURSE OF THE DISEASE REDUCING THE REQUIREMENTS FOR INTRAVENOUS FLUIDS, BED SPACE AND PROFESSIONAL CARE.

I HAVE CHOSEN ONLY A FEW OF THOSE WHO DESERVE TO BE RECOGNIZED, SINCE IT WOULD NOT BE POSSIBLE IN ANY REASONABLE LENGTH OF TIME TO TELL OF THE MANY WHOSE STORIES SHOULD BE TOLD. THEIR ACTIONS AND THEIR LIVES ENRICH OUR EFFORTS AS WE CONTINUE TO SERVE THE SAME PURPOSES THAT MOTIVATED THEM.

AN OCCASION OF THIS KIND--AN AWARDS CEREMONY--IS A REMINDER THAT SUCCESSES CONTINUE TO BE REALIZED AND THAT, IN

FACT, THE PACE OF PROGRESS IS ACCELERATING. THE FUTURE OF NIH IS BOUND TO BE EXCITING INDEED.

TO EACH OF TODAY'S HONOREES, THEIR FAMILIES AND FRIENDS, I WISH TO EXTEND MY WARMEST CONGRATULATIONS, AND ON BEHALF OF ALL OF US, HEARTY THANKS.

SOME THOUGHTS ON THE FUTURE OF SPACE LIFE SCIENCES RESEARCH*

BY

JAMES B. WYNGAARDEN, M.D.**

Good afternoon. It is a pleasure to participate in this first Space Life Sciences Symposium.

As the National Aeronautics and Space Administration (NASA) embarks on the second quarter-century of space exploration, it is heartening to note the spirit of cooperation that has characterized the current effort to chart the future course of space life sciences research.

- The NIH, for instance, welcomes the opportunity to participate with NASA in a joint working group that has been established to provide a focus for the planning and coordination of programs and activities related to space medicine and serve as a point of liaison with other Federal agencies and non-Federal organizations.

- And, I have been pleased to share my views with representatives of the NASA Life Science Strategic Planning Study Committee that, under the chairmanship of Dr. Frederick Robbins, is attempting to develop a set of recommendations that can serve as a framework for space life sciences research for the next decade, and beyond.

- In addition, NIH is participating in the "Quick is Beautiful" Task Force that is attempting to identify and examine proposals for high-quality scientific investigations that can be planned and conducted in a relatively short time span aboard the Space Station.

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*PRESENTED AT THE SPACE LIFE SCIENCES SYMPOSIUM LUNCHEON
OMNI SHOREHAM HOTEL, WASHINGTON, D.C., JUNE 23, 1987.

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The results of these activities should provide a more refined basis for program development. In the interim, however, as a result of experience gained during the Shuttle era and through continuous, informal assessments of advances in the state of knowledge in the life sciences related to space exploration, there does exist a set of broad goals, opportunities, and strategies for space life sciences research.

And the experience gained over the last four or five decades in providing support to establish and maintain the preeminence of the scientific enterprise in this country has served to establish a set of general principles of research support that could serve to guide the development of a national program of space life sciences research.

I would like to offer some observations on both of these points.

First, it seems clear that unprecedented opportunities exist for exciting research across the full spectrum of the space life sciences. For instance,

- The relatively new science of exobiology--which combines elements of astronomy, biology, chemistry, geology, and engineering--is now capable of addressing some of the most profound questions concerning the origin, development, and distribution of life in the universe.

- The advent of the Space Shuttle has provided the first practical and effective way of separating the effects of gravity from other physiological changes that occur over time and has permitted a new level of sophistication in investigations in gravitational biology. The Space Station will undoubtedly provide an expanded capability to explore, by inference from experiments conducted under weightless conditions, the complex and fundamental relationship between gravity and life on Earth and the adaptation of living organs to the space environment.

- Biospherics research has begun to focus on the ways in which living and non-living components of the Earth are interrelated through a complex interplay of physical, chemical, and biological processes. An enormous challenge lies in the task of compiling and correlating biological,

geological, chemical, oceanographic, and meteorological data on a global scale to determine laws governing the constant cycling of living and non-living material throughout the biosphere.

o As longer space flights are contemplated and the need increases for technology to regenerate air, water, and food supplies aboard manned spacecraft, the need increases for research leading to the development of practical methods for the synthesis of fats and carbohydrates from carbon dioxide and water, the perfection of techniques for culturing higher plants and algae, and the design of processes that are feasible for recycling solid and liquid waste within the space craft enviromnent.

o And, in the area in which I am more intimately involved--biomedical research--it is clear that space travel is creating a new variety of challenging health problems that are now just beginning to be perceived and which undoubtedly will continue to emerge as man is exposed to the specialized environment of space for increasingly longer periods of time.

o From the rather limited experience with relatively short space flights, it appears that the body undergoes profound physiological changes as a result of the microgravity environment that exists in space.

- One immediate effect of microgravity is post-flight orthostatic intolerance (the microgravity-induced changes in the cardiovascular system that can cause fainting or dizziness and difficulty in maintaining an upright posture when gravity is reimposed during reentry and landing).

  While preliminary results suggest that the cardiovascular system can adjust fairly quickly to fluid shifts and a loss in blood volume, extensive additional investigation will be required to determine the long-term adaptation of the cardiovascular system to weightlessness.

-- Another pronounced effect of microgravity is the loss of bone minerals, such as calcium and phosphorus, that takes place as bone resorption occurs faster than bone formation during space flight. This condition increases greatly the risk of skeletal fracture and the formation of kidney stones.

   Clearly, further research is needed to understand the effects of microgravity and prolonged immobilization on the human musculoskeletal system.

-- One of the most bothersome problems detected early in space flight is the Space Adaptation Syndrome (or space motion sickness), a debilitating neurophysiological problem that is believed to result from conflicting signals sent by the balancing organs of the inner ear, the eyes, and the muscle sensors.

   Before measures can be devised to reduce or prevent the lethargy, severe headaches, and vomiting associated with motion sickness in space, much more must be learned about the neurovestibular system and the mechanisms by which this system is distrurbed during space flight.

-- The most significant limitation to long-term space missions could conceivably be the health hazard posed by exposure to ionizing radiation; particularly from high energy, heavy particles emanating from the sun and galaxy.

   Additional research will be needed to assess the relative biological effectiveness of these particles and to develop agents to reduce or alleviate the biological consequences of exposure to these agents.

These are but a few examples of areas that will require further study in order to provide a sound conceptual basis for future advances in space medicine.

In addition to protecting the health of space travelers, the NIH has another equally important reason for maintaining a strong interest in space medicine which stems from the potential contribution that research in space can make toward achieving the traditional mission of the NIH in dealing with health problems on Earth.

- The novel environment encountered in space provides a special "laboratory" in which studies and procedures can be performed that would be exceedingly difficult or impossible to achieve on the surface of the Earth.

- Access to the space environment provided by Spacelab and Space Station can be expected to provide especially rewarding opportunities for studies in neurophysiology, immunology, and developmental and reproductive biology.

Principles of Research Support

As many of you may know, the NIH is currently observing its 100th anniversary. The occasion is being marked by a year-long series of seminars, conferences, symposia, receptions, radio and television broadcasts, an NIH alumni reunion, and a variety of events here and in many locations across the United States, and in other countries, providing public recognition of the role of NIH in what is being described as "A Century of Science for Health."

In reflecting on the rich history that has been forged during this century of science we at NIH take special pride in that chapter written by Dr. Joseph Goldberger, a scientist whose entire career--from 1899 to 1929--was spent in the Public Health Service Hygienic Laboratory, that in time became the National Institutes of Health.

Dr. Goldberger conducted his classic investigations of pellagra during a period when conventional wisdom held that this devastating disease had an infectious origin that was in some way related to sanitary conditions. His intensive examination of the literature, keen observation, and remarkkable epidemiological investigations caused him to take public issue with the

widespread assumption that pellagra was a communicable disease and, in fact, led him to conclude that this disease was caused by a nutritional deficiency.

- In public institutions where the disease occurred, he was able to demonstrate that generous amounts of milk, eggs, meat, beans, and peas prevented it. Yet, physicians who were treating pellagra at the time persisted in their belief that it was caused by an infectious organism.

To counter this skepticism, Goldberger and one of his associates injected each other with blood from a pellagra patient. Later, he and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife. None contracted the disease. However, the doubts about Goldberger's findings persisted and were not refuted until after his death.

- In 1936, nicotinic acid was identified as the pellagra-preventive factor. Today, pellagra has been virtually eliminated through simple, safe, and effective means for cure and prevention.

In my mind, this chapter in the history of science demonstrates the spirit of adventure, the courage to challenge dogma, and the willingness to accept personal risk that was characteristic of so many of our scientific forefathers and continues to find expression in the eagerness with which the current generation of astronauts and space scientists embraces new challenges that present themselves today.

This centennial year also serves as an occasion to reflect on the events that have shaped the course of biomedical research in this country and to observe the lessons that can be learned from this long history of science support that might be useful also in guiding the future development of space life sciences research.

Against this backdrop, my experience convinces me that:

- Progress in advancing social goals and achieving categorical objectives is entirely dependent upon the establishment of an adequate base of knowledge in the underlying areas of science, and

  -- To mount major initiatives in the absence of this requisite science base is wasteful of precious scientific manpower, facilities, and funds and creates public expectations that cannot be met.

- The best hope for significant progress in basic research continues to be through the efforts of individual investigators pursuing their own ideas in response to the dictates of the internal logic of science and not in response to the demands of narrow categorical objectives.

  -- In this regard, it is essential to provide a steady and predictable level of funding for basic research through the support of investigator-initiated research project grants awarded on the basis of national competition and judged by panels of peers drawn from the ranks of non-Federal research organizations.

- We must address the issue of the role of "big science" in biology by devising appropriate ways to achieve a balance between the need which exists to maintain an adequate level of support for free-ranging, investigator-initiated research and the needs to mount major initiatives in response to emerging opportunities that, by their intrinsic nature, call for large-scale, highly organized, and centrally directed activities requiring sophisticated equipment, extensive information processing, and the sharing of large, specialized facilities.

- Support for research training must be provided at levels sufficient to assure a continuous supply of scientists trained in areas appropriate to meet our national research needs.

- We cannot afford to continue to ignore the declining health of the research institutions in which the bulk of basic research in this country is conducted.

-- A concerted effort must be made to address the growing need to find appropriate ways to strengthen and maintain the research infrastructure by overcoming shortages and obsolescence of research instrumentation and correcting for the physical deterioration of laboratories, animal buildings, and other research facilities.

o Simplification must be achieved in the Federal system of sponsored research to reduce the administrative burden associated with the conduct and management of research to the absolute minimum consistent with the appropriate stewardship of public funds.

o Every effort must be made to restore and maintain public confidence in the support of research by promoting the highest personal standards of integrity among scientists and assuring the proper care and use of animals used in research.

-- There is also a critical need to develop a better understanding among the mass media, elected officials, and the general public of the scientific imperative of using animals in research.

-- The current attacks on biological research must be taken seriously and responded to with scientific fact and evidence of the strength of our commitment to the pursuit of important goals through responsible use of animals in research, including space life research.

Conclusion

My remarks, today, were intended largely to convey the sense of optimism and anticipation I feel concerning the vast array of scientific opportunities that exist in space life sciences research, to suggest some elements of a broad research strategy that might be considered in charting the future course of this research, and to note some of the problems and concerns that might be encountered as we proceed to carry out this program strategy.

We have a rich legacy to draw upon in dealing with the current set of challenges, and I am confident that--as in the past--we will exercise the resourcefulness necessary to advance space life sciences research and bring its benefits to the attainment of the national goals that have been set before us.

REMARKS*

BY

JAMES B. WYNGAARDEN, M.D.**

IT IS A HAPPY CIRCUMSTANCE THAT IN THE CLOSING MONTHS OF THE FIRST CENTURY OF THE NATIONAL INSTITUTES OF HEALTH WE ARE LAUNCHING A NEW ORGANIZATIONAL ENTITY THAT WILL BECOME AN IMPORTANT PART OF THE HISTORY OF OUR SECOND CENTURY. TODAY'S CEREMONY MARKS THE COMPLETION OF THE ESTABLISHMENT OF THE NATIONAL CENTER FOR NURSING RESEARCH AS A CONSTITUENT UNIT OF THE NIH. THE CENTER WAS TECHNICALLY CREATED BY THE SECRETARY OF HEALTH AND HUMAN SERVICES ON APRIL 18, 1986, SOON AFTER THE PASSAGE OF THE HEALTH EXTENSION ACT OF 1985. TWO MONTHS LATER THE PERSONNEL, THE BUDGET, AND THE GRANT PORTFOLIO OF THE NURSING RESEARCH SECTION OF THE HEALTH RESOURCES AND SERVICES ADMINISTRATION WERE TRANSFERRED TO NIH. THE NATIONAL ADVISORY COUNCIL OF THE CENTER WAS APPOINTED AND CONVENED ON FEBRUARY 17, THIS YEAR. SHORTLY THEREAFTER THE FIRST DIRECTOR WAS NOMINATED AND APPROVED, AND TODAY WE WILL ADMINISTER THE OATH OF OFFICE TO THAT DIRECTOR, DR. ADA SUE HINSHAW.

I WOULD BE REMISS ON THIS OCCASION NOT TO MENTION THE SKILL AND DEVOTION WITH WHICH DR. DORIS MERRITT PAVED THE WAY

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*PRESENTED AT THE SWEARING-IN OF DR. ADA HINSHAW AS FIRST DIRECTOR OF THE NATIONAL CENTER FOR NURSING RESEARCH, JUNE 24, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND

FOR INTEGRATION OF THE CENTER INTO FULL MEMBERSHIP WITHIN THE NIH FAMILY.

THE MULTIDISCIPLINARY NATURE OF NURSING RESEARCH IS EVIDENT IN THE SCOPE OF THE SUBJECTS OF EXISTING AWARDS THAT WERE MADE BY THE CENTER DURING FISCAL 1986. INCLUDED IN THE COMPASS OF NURSING RESEARCH ARE SCIENTIFIC INQUIRIES INTO FUNDAMENTAL BIOMEDICAL AND BEHAVIORAL PROCESSES RELEVANT TO NURSING, STUDY OF THE APPLICATIONS OF NURSING INTERVENTIONS TO PATIENT CARE, AND STUDIES RELEVANT TO INDIVIDUAL RESPONSIBILITY FOR WELLNESS AND THE DIAGNOSIS, TREATMENT, AND PREVENTION OF DISEASE

THE NATIONAL CENTER FOR NURSING RESEARCH HAS ALREADY INITIATED CAREER DEVELOPMENT AWARDS FOR THE GROWING NUMBER OF NURSE SCIENTISTS, AND IS EMPHASIZING INDIVIDUAL POSTDOCTORAL TRAINING OPPORTUNITIES IN ESTABLISHED NIH-SUPPORTED RESEARCH AND DEMONSTRATIONS CENTERS AND IN OUR INTRAMURAL RESEARCH PROGRAMS. IN ORDER TO AUGMENT THE CONTINUING DEVELOPMENT OF CENTERS OF EXCELLENCE IN NURSING RESEARCH, NCNR WILL PROVIDE INSTITUTIONAL RESEARCH TRAINING OPPORTUNITIES FOR BOTH PRE AND POSTDOCTORAL TRAINEES. THE NCNR WILL GIVE PRIORITY TO INVESTIGATOR-INITIATED RESEARCH IN NEW AND EMERGING, HIGH-PRIORITY AREAS: SUPPORT OF HEALTH PROMOTING BEHAVIORS, EMPHASIS ON DISEASE PREVENTION, THE CARE OF THE AGING POPULATION, COPING WITH IATROGENIC EFFECTS SECONDARY TO NECESSARY AND LIFESAVING THERAPIES, ALTERNATIVE MEASURES FOR

PROVIDING NURSING INTERVENTIONS FOR PATIENTS AND FAMILIES OF INDIVIDUALS WITH AIDS AND ALZHEIMER'S DISEASE, AND THE ETHICS OF DECISION MAKING IN THE CLINICAL ENVIRONMENT.

WHILE CONTINUING TO EXPLORE THE SOCIAL AND BEHAVIORAL PARAMETERS OF GOOD HEALTH, THE CENTER IS INCORPORATING THE NIH OUTLOOK AND METHODOLOGY IN THE SEARCH FOR THE BIOCHEMICAL AND PHYSIOLOGICAL BASES OF CARE. NURSING SCIENCE WILL TAKE ITS PLACE BESIDE AND AS A COMPLEMENT TO THE TRADITIONAL BIOMEDICAL SCIENCES.

THE FRUITION OF A NATIONAL PROGRAM OF THIS SCOPE AND IMPORTANCE WILL NOT OCCUR INSTANTANEOUSLY. METHODICALLY AND WITH CAREFUL ATTENTION, UNDER THE LEADERSHIP OF ITS DIRECTOR, WITH ADVICE OF ITS COUNCIL, AND THE SUPPORT OF THE NURSING RESEARCH COMMUNITY, THE CENTER WILL ACT TO ACCELERATE THE DEFINITION AND SHAPE OF THE FUTURE OF NURSING SCIENCE AND THE ARTICULATION OF A NATIONAL RESEARCH PLAN.

IN OUR SEARCH FOR A DIRECTOR WE WERE GRATIFIED WITH THE PANEL OF EXCELLENT CANDIDATES. FROM THAT GROUP DR. ADA SUE HINSHAW WAS OUR UNANIMOUS CHOICE. SHE BRINGS TO THE POSITION OF DIRECTOR THE PROFESSIONAL QUALIFICATIONS AND PERSONAL QUALITIES SO NECESSARY FOR THE NURTURE AND SUCCESSFUL DEVELOPMENT OF THE CENTER. THE HIGH REGARD IN WHICH SHE OBVIOUSLY IS HELD BY HER PROFESSIONAL AND SCIENTIFIC PEERS NATIONWIDE ADDS A FOUNDATION OF GOODWILL AND TRUST IN THE

EXTRAMURAL COMMUNITY THAT WILL PROVE TO BE OF EXTREME VALUE TO THE CENTER.

A CHARTER DIRECTOR HAS UNUSUAL RESPONSIBILITY AND OPPORTUNITY IN SHAPING THE FUTURE COURSE OF AN ORGANIZATION, AND WE ARE PARTICULARLY FORTUNATE THAT DR. HINSHAW OCCUPIES THAT CRITICAL POSITION AT THE INITIATION OF THE NATIONAL CENTER FOR NURSING RESEARCH.

UNDER HER LEADERSHIP I AM CONFIDENT THAT THE CENTER WILL CONTINUE TO GROW RAPIDLY AND THAT IT WILL CONTRIBUTE SUBSTANTIALLY TO THE ACCOMPLISHMENT OF THE OVERALL MISSION OF THE NIH.

IT IS WITH THE GREATEST PLEASURE, DR. HINSHAW, THAT WE WELCOME YOU TO THE NATIONAL INSTITUTES OF HEALTH AS THE DIRECTOR OF THE NATIONAL CENTER FOR NURSING RESEARCH.

I WILL NOW ADMINISTER TO YOU THE OATH OF OFFICE.....

REMARKS*

by

James B. Wyngaarden, M.D.**

I consider it a great privilege to be present at this symposium being held to mark the establishment of the NIH Alumni Association in Japan, and in commemoration of the 100th anniversary of the National Institutes of Health. I offer you my warmest congratulations for the success of your organizational effort. Personally and on behalf of all my colleagues, I extend sincere thanks for your interest in the continued progress of the NIH.

Groups of alumni in various cities in the United States have set up organizations for centennial activities, but the NIH Alumni Association in Japan is the first such association of former NIHers in another country.

I will take this opportunity to tell you of some of the exciting centennial events that have taken place, and some that are to come, and to recount briefly some of the history of NIH.

As many of you know, we began a year-long observance of our hundredth year with a ceremony in Bethesda last October, attended by all of the living former directors of the NIH, by the U.S. Secretary of Health and Human Services, and by some of the members of Congress who have been strong champions of the NIH, helping us to gain necessary support for our programs over the years.

Also participating in the opening ceremonies were Dr. Roy Vagelos, Chief Executive Officer of Merck and Company, and Dr. Daniel C. Tosteson, Dean of the Harvard Medical School. The presence of Drs. Vagelos and

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*Presented at the NIH Alumni Association in Japan Symposium, Tokyo, Japan, June 30, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

Tosteson was an expression of one of the central themes of the NIH centennial observance--that is, the partnership of industry and academia with the government in conducting and supporting biomedical research.

Another of the principal themes of the NIH centennial is to use the occasion to remind young people of the challenges, excitement and rewards of careers in biomedical research. To symbolize this purpose the NIH invited the governors of each of the states and territories of the United States to select an outstanding high school student to come to Washington for three days of briefings from some of our leading scientists, and for visits to the NIH campus, as well as to major facilities and places of historical interest. Each student was asked to select the teacher who had been of the most influence in his or her school career. The teachers accompanied the students on the trip, which took place over the weekend of February 28. It was a highly successful event. We were especially pleased that 17 Nobel laureates gave generously of their time, joining the students at two informal occasions. These opportunities for the young people to talk with some of the world's leading scientists were highly valuable experiences.

Another centennial activity that has been highly successful is a series of seven breakfasts for members of Congress and their staffs. At each of these events leading scientists give brief discussions of health related research topics of current interest. Next week the subject will be "Advances in Aging Research."

A final series of centennial events will take place in Bethesda October 15-18 this year. This three-day weekend of scientific symposia and an alumni reunion will be the culminating event of the NIH centennial observance. The topics of the symposia range across the spectrum. For example, the first one on October 15 will be on "Biochemical Foundations of Medical Research." The list of speakers includes Dr. Osamu Hayaishi of Osaka. Other symposia on the first day include a session on molecular biophysics, and one on "Milestones in Medicine."

Topics of the second day symposia include genetics and molecular biology, oncology, infectious diseases, developmental biology, receptors, immunology, cardiology, cell biology, and endocrinology.

The plenary symposium, to be held in the Kennedy Center on October 17, will have as a general title, "Frontiers of Biomedical Research." I have described the symposia in some detail because we feel most fortunate to have been able to assemble such an outstanding group of scientists.

The official centennial ceremony will be held on Friday, October 16. President Reagan has been invited to speak. Other distinguished guests will be present, as will the alumni and NIH staff.

The NIH is using the centennial as an occasion for better informing the people of the United States of the importance of biomedical research as the foundation for improving health. During the fall the U.S. Public Broadcasting Service is to televise a four-part series of one-hour programs that will trace the developments in biomedical science and health care for the past century, and the role of the NIH in the astounding progress that has been made. At the same time, a book will be published by Doubleday and Company based largely on the material to be covered in the television programs.

Many of the centennial events and projects have been made possible by the generous support of 14 of America's pharmaceutical companies and the Howard Hughes Medical Institute. They have donated to the centennial fund substantial sums enabling us to carry out projects for which public funds could not be used.

Other organizations and groups have been generous in their support, thereby making possible other centennial activities, just as the NIH Alumni Association in Japan has done.

Earlier I mentioned that a major theme of our centennial observance is the partnership of government, academia and industry that has developed

over the past century for the support and conduct of biomedical research--a relationship that has grown stronger in recent years and that promises to continue unabated the extremely rapid rate of progress in the biosciences that has been characteristic of the past two decades.

The partnership as we know it today is of relatively recent origin.

For the first half of its history, the NIH was a small government laboratory. At the beginning the entire operation was housed in an attic room of the Marine Hospital Service facility on Staten Island in the Port of New York.

The Laboratory had been set up at a total cost of about $300 by Dr. Joseph J. Kinyoun in 1887. Its purpose was to search for ways to prevent the spread of cholera, yellow fever and other diseases. In 1891 the Laboratory was moved to temporary quarters in Washington, and in 1904 to new buildings in downtown Washington where it remained until 1938. While there had been gradual growth, the total staff of the NIH in 1937, its fiftieth year, was less than 200.

After moving to a large campus outside of Washington in Bethesda, Maryland, in 1938, the NIH began to grow in numbers of personnel and in facilities.

In the following decade a change took place in NIH that had a marked effect on biomedical research in the United States, and to a considerable extent throughout the world. The simplest description of the change would be to state that it was the establishment of our partnerships for research with many American universities, medical schools, hospitals and other research laboratories.

In 1945 the NIH was assigned responsibility for administering the ongoing biomedical research grants and contracts that had been awarded previously to non-Federal laboratories by the wartime Office of Scientific Research and Development. This assignment reflected a decision by the

U.S. Government to greatly expand its peacetime sponsorship of biomedical research.

It also marked a decision that the NIH would become the principal biomedical research arm of the Federal Government. Since that time the numbers and amounts of grants and contracts have continued to grow so that almost 90 percent of the NIH budget today is devoted to the support of research and research training through more than 28,000 grants and contracts at some 1600 academic centers, hospitals, and industrial and independent laboratories throughout the United States and in many other countries.

But as all our alumni know, an extremely important part of our research activities takes place in our own laboratories. Almost 3,000 doctoral level government scientists and as many as 3,500 trained support staff are engaged in our in-house research program. The intramural research activities are carried out in a great number of different research units, some with specific or targeted goals, and others that are allowed total freedom to pursue scientific clues wherever they may lead. Some of our laboratories are clinically oriented, and others are focused on basic studies as, for example, research in molecular biology. Through the years Japanese researchers have constituted a sizeable part of this scientific community as visiting co-workers.

Talented scientists from throughout the world come to Bethesda to share their knowledge and expertise with their fellow scientists. Distinguished scientists at all stages in their careers are invited to come to the NIH to conduct research in their own areas of interest and, if it is desired, to receive further training. Under what we call the Visiting Program, stipends are provided to the visiting scientist and each participant works closely with a senior NIH investigator who serves as sponsor or supervisor during the visitor's period of award or appointment. Currently over 1,100 scientists from 70 countries are participating in this program, including 267 from Japan.

Under another program for non-Federal scientists called the Guest Researcher Program, some 400 investigators are conducting research at NIH. Guest researchers do not receive stipends, but are provided laboratory space and research support. Currently 53 of our guest researchers are from Japan.

At this time, by far the largest group of NIH visiting scientists and guest researchers is from Japan. In all, since the beginning of our programs for visitors and guests in 1950, there have been 1527 Japanese participants in these programs.

On June 17 the NIH was honored with a visit on our Bethesda campus of a delegation from the Committee on Science and Technology of the House of Representatives of the Japanese Diet. The delegation, led by Mr. Shozo Harada, was briefed by one of our senior scientists who told them of our facilities and organizations, and particularly about research opportunities at NIH for visiting scientists other than Americans. The presence of this distinguished group gave us the opportunity to tell them how highly we value our Japanese scientific colleagues. They were pleased to learn of the numbers of visiting scientists and guest researchers who have come from Japan to participate in our intramural research program. The Japanese legislators were told of two mechanisms we use for the visiting scientists who do research at NIH--how both groups are provided laboratory space, equipment and supplies, but the visiting scientists are paid salaries by the NIH while the guest researchers are supported by their home institutions. The legislators were surprised at the amount of U.S. funds expended for salaries of Japanese scientists (something over $4 million roughly). The legislators were told about concerns in the U.S. Congress regarding the increasing number of scientists from other countries who are conducting research at NIH. It was suggested to the guests that greater use of the guest researcher mechanism would be helpful in assuring the continuation of collaboration in the future.

Because the members of the Alumni Association are familiar with the intramural program of the National Institutes of Health, and in fact could still be considered to be a part of it, I think the members of the audience

who are alumni will indulge me as I read a very complimentary description of that program. It was written by the well-known President Emeritus of the Memorial Sloan Kettering Cancer Center in New York, Dr. Lewis Thomas. The statement was a part of the introduction to a book containing the personal accounts of a number of NIH intramural scientists. He wrote of the flourishing program of grant and contract awards, and then Dr. Thomas observes, "But at the center of the NIH scientific effort, driving the whole vast enterprise along, is the research conducted on the Bethesda campus itself--the so-called Intramural Research Program." He then said, "Although this represents only a minor portion of the total NIH budget--around 10 percent--for sheer excellence and abundant productivity, the Institution cannot be matched by any other scientific enterprise anywhere."

Of special relevance to all NIH alumni was Dr. Thomas' next comment which I will read in full.

"One aspect of the intramural program deserves special mention and emphasis. It is a training ground for young investigators,....that the Institution has achieved its most singular influence. For three decades the youngest and brightest candidates for careers in biomedical research have competed for the opportunity to learn how to do science in this place. Most of them worked here for two or three years and then deployed out to the universities to continue in research, and a high percentage of these alumni then turned into the country's leaders of academic science."

Then his final tribute, "It has, in short, been a success story from start to finish, although the "finish" is, I trust, nowhere near. The NIH laboratories are something for the Government to boast about, to dine out on, and to be immensely proud of. It is my hope that the same intelligence and scientific good taste will be displayed for the Institution's future as was used to build the magnificient instrument now at hand."

I believe that sense of pride is felt by each of us as NIH alumni, and in your presence I have felt comfortable in speaking unabashedly about the remarkable organization that is our common bond across many thousands of miles.

THE SCIENCE AND TECHNOLOGY POLICY OF THE UNITED STATES AND THE ROLE OF NIH*

by

James B. Wyngaarden, M.D.**

I am honored to have been asked to address this distinguished audience. It was suggested that I speak on the science and technology policy of the United States. In doing so I will also tell you some things about the history of the National Institutes of Health for it is an expression of the policy of our government with regard to science and technology.

As recently as 1945, Vannevar Bush, Science Advisor to President Roosevelt, made the blunt statement, "We have no national policy for science. The government has only begun to utilize science in the nation's welfare. There is no body within the government charged with formulating or executing a national science policy. There are no standing committees of the Congress devoted to this important subject. Science has been in the wings. It should be brought to the center of the stage--for in it lies much of our hope for the future....We are entering a period when science needs and deserves increased support from public funds."[1]

This arresting statement was made in a special report to the President titled "Science: the Endless Frontier." The document was to have substantial influence on decisions made by our Federal Government since 1945 and particularly with regard to the development of the modern National Institutes of Health.

In the past four decades, science has indeed been brought into center stage in the United States. Substantial public funding now is provided for the support of many different kinds of research, with special emphasis on

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*Address presented at the National Cancer Center, Tokyo, Japan, July 2, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

basic research. A number of major congressional committees have been established specifically for the encouragement and oversight of Federal scientific and technological activities. A science advisory committee has been set up with direct responsibility for keeping the President and the central Office of Management and Budget informed and advised regarding scientific issues and opportunities. The National Science Foundation has been created at cabinet level with the mission "to promote the progress of science and engineering through the support of research and education programs. Its major emphasis is on high quality, merit-selected research, the search for improved understanding of the fundamental laws of nature upon which our future well-being as a nation depends."[2] The National Science Foundation also supports applied research in several areas and its educational programs are aimed at ensuring increasing understanding of science and engineering at all educational levels and an adequate supply of scientists and engineers to meet our country's needs.

The National Science Foundation and the National Institutes of Health have similar responsibilities but in different areas of science, with the NIH assigned a broad mission in biomedical research. Both agencies support research through grants, contracts and other agreements awarded to universities and other research organizations. Unlike the NSF, the National Institutes of Health conducts a large amount of research within its own laboratories.

These and other research agencies are expressions of the science and technology policy of the United States. That policy, however, is not to be found in an article in the U.S. Constitution nor is it fully stated in an existing body of statutes.

The most recent comprehensive examination of our national policy on science took place during the previous session of Congress. A Task Force on Science Policy of the Committee on Science and Technology of the United States House of Representatives conducted a long series of hearings and an exhaustive study of current scientific activities in our country. Some 22

volumes of testimony have been published. From the reports of these hearings will emerge a detailed description of science and technology in this period of our nation's history.

But the active science technology policy of our Government is stated and described annually in the appropriations process, when funds are provided for the support of all Government agencies. In the President's budget message to the Congress with his proposals for the many Federal agencies, a justification is given for each general class of expenditure. In recent years the budget document has contained general comments from the President as to his reason for requesting funds for scientific research. These comments together with the specific actions taken by the Congress with respect to the different scientific agencies constitute an up-to-the-moment statement of the science and technology policy of the United States.

In justifying his request for funding for Federal agencies for Fiscal Year 1988, President Reagan's budget message stated:

"The Federal Government supports research and development:

> To assist in meeting broad national needs, particularly where the private sector lacks sufficient incentives for adequate investment to assure long-term economic growth and continued improvement in the quality of life for all citizens. Examples of such research and development include Federal investments in basic research across all fields of science and engineering and agricultural and health-related research and development."[3]

In a summary the budget document pointed out that the 1988 budget not only calls for added support for research and development to meet national needs, it "also provides for basic research, particularly at universities to help generate the new knowledge necessary for continued technological innovation and to help assure the future availability of high- quality scientists and engineers..."[3] Significantly, the statement added that "Interdisciplinary basic research will receive special emphasis since research at the junction of disciplines can lead to the creation of important new fields of science. The Federal Government will also increase

efforts to help encourage the transfer to the private sector of technology and new knowledge created in Federal laboratories."

This statement is an example of the strong emphasis that the United States Government has placed on enchancing the support of basic research across all scientific and engineering disciplines. Even in a financially austere environment support for basic research, especially at universities, is an important factor in generating new knowledge to ensure continued technical innovation. It is regarded by our Government as an essential investment in the nation's future.

Because the private sector has had insufficient incentives to invest in such research, the Federal Government has for the past 40 years assumed an increasingly greater role in the support of basic research.

It is interesting how the language of the President's budget message for 1988 echoes the language of the 1945 Bush Report from which I quoted a moment ago. President Reagan's message spoke of increased support for basic research, particularly at universities. Forty years ago Vannevar Bush noted that, "The publicly and privately supported colleges, universities and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge to those who can apply it in government, in industry and elsewhere."[1]

Another description of the philosophy underlying the science and technology policy of the United States appeared in a report issued in 1965 titled "Basic Science and the National Goals." The report had been requested by the Committee on Science and Astronautics of the U.S. House of Representatives. The chapters of the report were written by some of the leaders of American Science. Professor Harvey Brooks of Harvard wrote the section on basic science. He spoke of the four distinct functions of basic research as a government activity. These functions, he stated, are cultural, economic, social and educational.

With regard to the cultural significance of basic research, he said, "(it) is recognized as one of the characteristic expressions of the highest aspirations of modern man. It bears much the same relation to contemporary civilization that the great artistic and philosophical creations of the Greeks did to theirs, or the great cathedrals did to medieval Europe. In a certain sense it not only serves the purposes of our society, but is one of the purposes of our society."[4]

Regarding the economic dimension of basic research, Dr. Brooks noted that "there is now general acceptance among economists of the importance of technical innovation in economic growth. To an increasing extent such innovation depends upon the results of basic science."[4]

As to the social significance of basic research, he pointed out that there is a recognized Federal responsibility for public health, and that in this area the Federal Government has been quick to utilize research in support of its mission, including a substantial amount of basic research.

In his comments on basic research and education, Dr. Brooks spoke of how in recent years the intimate connection between the two has been stressed. He reminded the Congress, however, that in engineering, medicine, agriculture and several other areas applied research is equally as important as advanced training. He mentioned that the healthy flow between basic and applied science has been one of the characteristics of American science contributing to its vitality.

Rather than quote further from the various reports and documents descriptive of American policy toward science and technology, I will relate to you some of the history of the National Institutes of Health, and in the light of that history can be seen a specific expression of Federal policy toward science as it has developed over a long period of years.

When Vannevar Bush said, some 40 years ago, that there was no science policy, he was referring to the fact that although our Government had long been interested in scientific matters Government scientific agencies had been extremely limited in function and that there was no common interest

and concern about science as a Government responsibility. The modern NIH came into being during that period.

We are now well beyond the mid point of a year-long observance of the 100th anniversary of the establishment of the National Institutes of Health in a one-room laboratory in the attic of the Marine Hospital facility on Staten Island in the Port of New York. This event occurred in August 1887.

The 1880s were years in which there was general ferment in the sciences. It was a time of solid scientific advances, particularly in biology, chemistry and physics. But almost all of the action was in Europe. Studies of the new discipline, bacteriology, were being carried out in Berlin and Paris by Robert Koch and Louis Pasteur, and their work exerted a pervasive influence on European scientists. When, in the early 1880s, American health authorities became deeply worried about the possibility that cholera might be imported into the United States, a young doctor, Dr. Joseph Kinyoun, was sent to study with Pasteur and Koch. Upon his return he set up a bacteriological laboratory at the Marine Hospital facility. That laboratory ultimately became the National Institutes of Health.

In the course of the intervening century, the NIH has undergone many organizational changes, one amounting almost to a transformation. For the first half of its history the agency was, in essence, a small Federal laboratory carrying out within its own confines important research projects, but its resources were such that at any given time only a limited number of studies could be conducted. It was during the adjustment period following World War II that the near-transformation took place. With demobilization, the Office of Scientific Research and Development went out of business on December 31, 1945, and some 250 biomedical research projects then being funded by the OSRD at universities, hospitals, and other research institutions were transferred to the NIH for administration. It is significant that the research projects were not cancelled, and that instead a mechanism was put in place for continuing to award such grants. Peacetime reliance on non-Federal laboratories for the conduct of federally-supported research represented a major change in Federal science policy. Possibly it is more

accurate to say that the Federal Government was beginning to create a coherent science policy following the paths suggested by Vannevar Bush. In any case, this change had the dual effect of confirming NIH's role as the principal biomedical research arm of the Government, and establishing extramural grants as the dominant mechanism for the support of such research.

Today, almost 90 percent of the NIH's budget is devoted to extramural awards for research and research training and the necessary administrative costs entailed.

More than 10 percent of our total budget, will be used this year for research in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural research program. The diversity of the program was described recently by one of our senior scientists, Dr. Maxine Singer, who told an audience of industrial scientists that "on the campus, we are divided up into all manner of units, some with targeted goals, some with total scholarly freedom, some with clinically oriented concerns, some with interests in basic biology that cover the gamut of living organisms and the whole range of biologically relevant questions from the synthesis of important organic molecules, computer applications, through the development of fly embryos, and the treatment of major diseases."[6]

Research training is an essential and integral part of our intramural research activity. We offer a variety of structured experiences for postdoctoral trainees in graduate and professional level programs in the clinical and basic sciences. At this time almost 900 trainees are participating in our regular training programs.

Above and beyond the regular training programs we conduct the NIH Visiting Programs for talented scientists from throughout the world, who come to Bethesda to share in the resources of the NIH. Through this program distinguished scientists at all levels of their careers are invited to receive further training or to conduct research in their biomedical specialities. Each participant in the visiting program works closely with

a senior NIH investigator who serves as sponsor or supervisor during the visitor's period of award or appointment. Currently over 1,500 scientists from 70 countries are participating in our visitors' programs. Japanese participants in these programs far outnumber the visiting scientists from any other country. As of June 1 there were 327 Japanese visiting scientists and guest workers at NIH. Since our visiting programs were initiated in 1950, there have been more than 1500 Japanese participants.

As large as the intramural program is, however, the largest part of NIH research today takes place in some 1600 universities, medical schools, hospitals, independent and industrial laboratories. Last year the NIH funded more than 28,000 research and research training projects involving approximately 50,000 non-Federal scientists.

The NIH provides support for research training through a variety of types of grants. Currently, more than 10,000 trainees are being supported through our different training programs at academic medical centers, research hospitals, graduate schools and laboratories throughout the United States.

The key mechanism used by NIH for support of biomedical research is the investigator-initiated project grant. It is used for supporting the majority of our extramural research. Well over half of our total budget is allocated to such projects for the conduct of research by non-Federal investigators. Such investigator-initiated research draws upon the expertise and intuition of practically the entire American scientific community. In recent years the number and quality of research proposals has increased steadily, so that even though our appropriations have increased from year to year, we are able currently to fund only just over one third of the meritorious grant proposals we receive each year.

With the rapid expansion of support for the extramural program, the number of applications for support grew even more rapidly. When the extramural program was first established it was recognized that it would be necessary to devise a sensitive and effective mechanism for selecting the most meritorious projects from the proposals for grants and contracts. The

system developed by the NIH for this critically important function has served well the interests of science and our health-related mission. The NIH peer review system has been emulated in a number of other countries.

The overall budget of the National Institutes of Health for Fiscal Year 1988 is now before the Congress, and at this point we are not discouraged but are not sure how encouraged to be. I will comment, however, that the 1987 budget of the NIH was increased overall about 17 percent over the FY 1986 budget. We recognize that an increase of this magnitude during a time of budget restraint is an indication of the level of confidence that exists in this country as to the long-term value of biomedical research. As in previous years, this continued generous support appears to result from an appreciation of the overarching importance of research that may lead to the development of new means for the prevention, treatment or cure of disease and disability.

The increase last year was larger than the gains in most years for the past two decades, but overall the growth has been continuous and substantial. During this same period industry has supplied an increasing share of national funding for health research and development. Twenty years ago industry as a whole was responsible for 24 percent of health research and development; in 1970 it had risen to 28 percent; by 1980 it was 31; and by 1986 industry's share had increased to 39 percent. Since the 1940s the NIH contribution to national health research and development each year had exceeded the total invested by all of industry until 1983. In 1986 the NIH share was about 35 percent.

Recent years have also seen the establishment of new ties between industrial organizations and some of the Nation's leading academic organizations for the purpose of expanding biomedical research activities. The NIH has an obvious interest in such new partnerships involving the institutions that for years have been closely linked with us through our extramural programs. We have not interposed ourselves in the new arrangements and have no intention of doing so.

Important li s between the NIH and industry were established more than 30 years ago with the development of the NIH patent policy that became the model for recent legislation applied to all Federal science agencies.

At different levels in the NIH programs there have been increasing interactions with industry. Provisions have been made to permit NIH scientists to lecture at and consult with industrial organizations, and guest investigators from industry may now be accommodated within the NIH intramural laboratories. We are now jointly sponsoring conferences for the direct exchange of scientific information between our scientists and their industrial counterparts.

The medical sciences have indeed made great strides throughout the world in the past 40 years. Fields such as genetics, virology, molecular biology, biochemistry and immunology have attracted the brightest and most productive investigators of our era. Discoveries have come so fast that it is almost impossible to keep up with these highly specialized fields. Newly developed instrumentation--taking us from vacuum tubes to transistors, to computer chips; from x-rays to CAT scans, to positron emission tomography and magnetic resonance imaging--has permitted amazing leaps in our fundamental understanding of human biology. In particular, scientific attention today is focused on the structural biology of organisms at the cellular and molecular level, and on the mechanisms by which they function properly or fail.

These are more than speculative or theoretical excursions. During this year, for example, the NIH has launched a new program in the structural biology of the AIDS virus, in a special effort to understand this virus at the most minute level of structure possible and to develop new types of drugs against it.

Today, scientists at NIH and elsewhere are also giving serious consideration to the wisdom of proposals to attempt to characterize the entire three billion nucleotide human genome. A decade ago this project would have been considered in many quarters to be science fiction. But the fact is that the technology for accomplishing it exists today. Whether

such an endeavor is practical, considering the resources available, is the question being debated.

There is general enthusiasm for proceeding. We are driven by curiosity, to be sure, but also by the belief that the secrets of the genes will greatly enlighten our quest for new insights about developmental biology, cellular regulation, and disease mechanism.

Consider, for example, that 4,000 human diseases have a genetic basis, including cystic fibrosis, Duchenne-type muscular dystrophy, Huntington's disease, and Alzheimer's disease. Such a project could result in discovery as to why some persons get diseases such as cancer, heart disease, mental illness, and others do not. Furthermore, such a project would provide an exponential increase in the knowledge of human biology.

In this effort, as well as in many others in basic science today, international cooperation is an essential element; in fact, in this particular project it is critical if chaos is to be avoided in dealing with the information generated from mapping and sequencing activities taking place in many parts of the world. Such seemingly small matters as adherence to uniformity of terminology can become a final determinant of the final success of the genome project.

There need be no better reason for conducting biomedical research than the improvement of human health. This is central to American policy regarding government support of such activities. In addition, there is the attraction felt by scientists for research as a means for meeting the insatiable human desire to know. This is certainly a consideration in connection with the genome project. In recent years, a third justification for Government support of research has come into prominence--biomedical research as a foundation for biotechnology. The Administration and the Congress in the U.S. have become interested in the economic consequences of our national investment in biomedical research that has been responsible for the emergence of biotechnology. Thus the subject has become an element of Federal policy that is in the process of being refined.

Biotechnology is not a new phenomenon of the 1980s--in fact, it has a long history, certainly as long as that of the NIH. A century ago, Louis Pasteur was engaged in research that changed, profoundly, the course of the biosciences and medicine. We sometimes forget how industry was also a direct object and beneficiary of a substantial portion of Pasteur's work. Perhaps the simplest way to describe this relationship is to cite the entry on Pasteur in the Encyclopedia Britannica, where his accomplishments are summarized in the following sentence. "Pasteur proved that microorganisms cause fermentation and disease; he originated and was the first to use vaccines for rabies, anthrax, and chicken cholera; he saved the wine, beer and silk industries of France and elsewhere; he performed important pioneer work in stereochemistry; (and) he originated pasteurization."[5]

A strikingly similar modern version of this catalog of accomplishments in biotechnology could be written about the direct and indirect benefits of basic research on molecular biology.

Biotechnology has had an impact on the conduct of basic biomedical research comparable perhaps to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology, clinical immunology and allergic response, and bone development and repair, just to name a few areas.

Biotechnology has created an unprecedented set of opportunities, issues and concerns in which the National Institutes of Health has more than a casual interest. This is because the body of knowledge on which the biotechnology industry is based was largely the result of sustained support for basic research in molecular biology and immunology provided by the NIH over the past few decades.

The NIH continues to make a major commitment to the future of biotechnology. The proportion of the NIH budget devoted to biotechnology has remained essentially constant for the past five years, with about 11 percent devoted to directly related research, and about 25 percent devoted

to underlying basic research and research training related to biotechnology.

About two years ago, at my suggestion, the NIH's principal advisory committee set aside a two-day meeting to discuss in a public forum the proper role for the NIH in the arena of biotechnology. The consensus was that we should continue to do what we do best, that is, to continue to conduct and support research and research training with continued emphasis on basic research.

That conclusion was similar to one reached at about the same time by the President's science advisor, George Keyworth, following a review of Federal science policy. He reported, "Perhaps the most important element of policy that emerged from recent reassessments was a renewed--and considerably strengthened Federal support for basic research. ....Quite simply, basic research is a vital underpinning for our national wellbeing."[6]

A more descriptive statement of the role of science in the life of people throughout the world appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads, "....To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability is of preeminent concern, and national policies concerning biomedical research is of surpassing importance in all countries. Its significance is truly universal, for as Disraeli said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."[7]

I will be glad to respond to any questions you may have.

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REMARKS*

by

James B. Wyngaarden, M.D.**

During this centennial year we often have been reminded of interesting chapters in the history of NIH. We have recalled the successes of the scientists and other leaders whose actions have been responsible for the remarkable first century of this remarkable institution.

A common thread runs through the accounts of these accomplishments--innovation. The very nature of research is to do and learn new things, and the "firsts" at the NIH are legion because our predecessors and contemporaries consistently have pioneered in the search for new knowledge. They also have been at the forefront in developing organizational mechanisms for fostering excellence.

At the time Dr. Kinyoun assembled the modest Hygienic Laboratory it was a "new thing." At the time the extramural programs were established they constituted a new peacetime partnership between government and academia. The NIH investigator-initiated project grant was a new mechanism that has served science extremely well. When the NIH system for peer review was established it was a "first."

At the time the Clinical Center was opened in 1953 it was recognized that special care must be exercised for the protection of patients, and a committee was established to review proposed projects that deviated from established practice or involved unusual hazards. The Center issued standards as to justifiable risks and procedures for informed consent. For years, the Clinical Center standards constituted the only written Federal policy on protecting human subjects, and it confirmed the status of NIH's research hospital as a leader. The Clinical Center became, in 1977, the first research institution to employ a full-time bioethicist.

So, Dr. John Fletcher is himself the first of a kind--and the new function he has performed so well is another in the list of innovations at NIH. In his tenure since 1977, he has defined the role of this new position--profession if you will--by his actions. Not only that, he exercises national leadership in making known the importance of ethics consultation in dealing with clinical research and care.

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*Presented at the Farewell Party for Dr. John C. Fletcher in the ACRF on August 11, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

Being the first is not usually an easy task. The purpose of John's appointment was not universally understood at the beginning and he encountered what he has neatly described as "complex responses." But in time he was able to demonstrate the value and benefit of his role as a teacher and consultant. John, you can leave knowing that you have joined the ranks of NIH pioneers, and that you have given definition to a new and important function within the NIH and throughout the research community.

You have our sincere thanks and best wishes as you enter a new phase in your valuable career.

OPENING REMARKS*

by

James B. Wyngaarden, M.D.**

It is a pleasure to open today's panel and to welcome our distinguished speakers. As part of NIH's Centennial Observance, it is important to take note of the role which NIH has played, together with others in our society, in ensuring adequate protection for the rights and welfare of individuals who participate as subjects of research.

In my remarks, I wish to touch on two points in setting out the theme of the panel: 1) the pivotal role of NIH in the history of protecting human subjects; and 2) the contribution of our unheralded collaborators in the research effort, those individuals who, as research subjects, give of their time and of themselves for their fellow human beings.

The modern history of protection of human subjects is often dated from the work of Claude Bernard, who published An Introduction to the Study of Experimental Medicine in 1867. That was twenty years before NIH came into being.

Bernard defined the mandate and the bounds of human experimentation. We have a "duty and right to perform an experiment" on humans he stated, but "never . . . an experiment which might be harmful . . . even though the results might be advantageous to science." Of course, Bernard could not have envisioned the complex research system of today -- worldwide multi-center clinical trials, P-3 facilities, cyclotrons, lasers, biological response modifiers, and recombinant DNA. No more than Joseph Kinyoun could have foreseen that today's NIH would grow out of a small room in an attic on Staten Island. But the vision of Claude Bernard still defines the moral landscape of research involving human subjects. And the NIH has been unstinting in its efforts to enlarge and enrich the horizons of that moral landscape just as it has worked to expand the scale and scope of research.

Nearly thirty-five years ago when the Clinical Center opened, NIH instituted the first Federal policy requiring prospective independent ethical review of research proposing to involve human subjects.

In the early 1960s, Dr. James Shannon, Director of NIH, took the lead in developing a set of ethical standards intended to be every bit as exacting in protecting research subjects as NIH's scientific standards

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*Presented at an NIH Centennial program, "The History of Research Involving Human Subjects," sponsored by the Office for Protection from Research Risks at the Lister Hill Center, Bethesda, Maryland, on September 8, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

were in ensuring the quality of research. These standards won endorsement as the policy of the Public Health Service in 1966, and later of the Department of Health, Education and Welfare, which promulgated them as regulations in 1974.

The 1970s and 1980s have proved to be a watershed era in exploring the full ethical implications of the revolution in biomedicine. The response was equal to the challenge: many feared that advances in biomedical research and technology would come at the expense of cherished human values but, in fact, our collective wisdom has found ways to address and resolve baffling ethical issues.

Often NIH took the lead on its own initiative, as in the case of the panel on the totally implantable artificial heart or in examining human gene therapy. On other occasions, as in the case of statutory commissions and departmental boards, the NIH has had a prominent role in helping to shape the response of our society to ethical questions arising in research and medicine.

For the last twenty years, NIH has had an established office, today known as the Office for Protection from Research Risks (OPRR), which is responsible for administering those regulatory and educational programs mandated under the PHS Act which are intended to safeguard the rights and well-being of human research subjects. OPRR has the actual responsibility as well, on behalf of the NIH and the Department of Health and Human Services, as lead agency in development and coordination of the Federal government-wide policy, modeled on the HHS regulations. I wish also to note the important contributions over the past ten years of the Office of Bioethics of the NIH Warren G. Magnuson Clinical Center. This office is responsible for ensuring the adequate protection of patients and volunteers in the NIH intramural program.

I have often phrased the reason for this longstanding involvement in ethical issues in the following way: Excellent clinical science must and does go hand in hand with the ethically sound and professionally responsible conduct of research.

The rationale for this is not surprising. Disease and ignorance diminish our human dignity. Fostering human dignity is what inspires research. As a world leader in scientific research, NIH engages daily in the effort to conquer ignorance and disease. It would be more than supreme irony, therefore, if scientific advances were made with some compromise of human dignity. It would be a betrayal of the imperative of Dr. Bernard's moral vision. The capabilities we now have in science make it necessary for us to enlarge upon the moral vision of Dr. Bernard. Each new breakthrough in science, each new promising lead to solve a riddle of nature summons a predictable response: explore the ethical implications. However, this phenomenon is not merely the fashion. It represents, I am convinced, the vigilance for which Bernard's imperative properly calls. For this reason, today's panel I expect will help us to be appropriately self-critical as well as, understandably, self-congratulatory.

I come now to my second point and with it I will conclude. The lessons of the last forty years have made us keenly aware of our responsibilities as researchers and as a society to the individuals who agree to take part as subjects of research in hope of furthering science. It is a tautology to say their contribution is indispensable to attaining the goals of biomedical and behavioral research. It is not merely an abstract "human dignity" that inspires and charges us in the field of research involving human subjects. It is our concern for the men, women, and children who generously agree to take on risks, even serious risks, to help benefit others. Seldom do they get accolades as heroes, though often they are heroic. Our society owes them an enormous debt. I do not believe you would find it presumptuous to take this occasion to acknowledge publicly our collective thanks.

DRAFT

NEW SCIENCE/NEW FRONTIERS*

BY

JAMES B. WYNGAARDEN, M.D.**

- It is a great pleasure for me to be here today to participate in this event commemorating the National Institutes of Health on its Centennial. Senator Weicker has long been a friend of NIH's and a stalwart supporter of biomedical research.

- Recognize statements made by Dr. Benno Schmidt and the other speakers and mention their past ties to NIH.

- Since 1887, when NIH was founded, the institution has been engaged in the challenges lying at the frontiers of science. One hundred years ago, Europe dominated science, the standard of excellence in medical science was found in the laboratories of Koch in Germany and Pasteur in France. American scientists were excited by the new discoveries in bacteriology but they were not really a part of them.

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*Presentation at the Colloquium Commemorating the NIH Centennial, Yale University, New Haven, Connecticut, September 9, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

DESPITE THE FACT THAT THIS COUNTRY WAS RAVAGED BY EPIDEMICS OF YELLOW FEVER, CHOLERA, AND TUBERCULOSIS (ALL THOUGHT TO BE BROUGHT INTO THE COUNTRY BY NEW ARRIVALS FROM EUROPE), MEDICAL PRACTITIONERS HERE WERE PAINFULLY AWARE OF HOW BACKWARD THIS COUNTRY WAS MEDICALLY. EFFORTS WERE MADE TO CONTAIN THE CONTAGION AT THE MAJOR PORT CITIES, BUT THESE WERE LARGELY INEFFECTIVE. THE ANSWERS CLEARLY LAY IN THE LABORATORIES ABROAD, IN THE NEW SCIENCE OF BACTERIOLOGY.

- NIH TRACES ITS ORIGINS TO A SMALL, ONE-ROOM ATTIC LABORATORY SET UP ON STATEN ISLAND, NY, AS A PART OF THE MARINE HOSPITAL SERVICE AND CALLED THE NATIONAL HYGIENIC LABORATORY. THE LABORATORY'S FIRST DIRECTOR, DR. JOSEPH KINYOUN, PURPOSELY MODELED HIS RESEARCH EFFORTS ON THE VANGUARD EUROPEAN WORK AFTER HAVING TRAVELED ABROAD TO LEARN THE NEW SCIENCE AND TECHNOLOGY BASED ON ZEISS' LATEST IMPROVED MICROSCOPES.

- JUST A FEW YEARS LATER, IN 1891, THE LABORATORY MOVED TO WASHINGTON, DC, UNDERSCORING THE STATUS OF THE LABORATORY AS A NATIONAL RESOURCE. IN THE YEARS TO COME, IT WAS THE SITE OF MANY HEROIC AND SUCCESSFUL BATTLES AGAINST DISEASE.

- AMONG THE SCIENTISTS ASSOCIATED WITH THE HYGIENIC

LABORATORY WERE SOME OF MEDICINE'S HEROES. FOR EXAMPLE, DR. HOWARD TAYLOR RICKETTS, WHOSE WORK ON ROCKY MOUNTAIN SPOTTED FEVER PROVIDED THE KEY FOR FINDING THE CAUSE OF ONE OF THE GREAT PLAGUES OF MANKIND--EPIDEMIC TYPHUS. RICKETTS DIED OF TYPHUS IN 1910, A VICTIM OF THE ORGANISM THAT HE HAD EARLIER DESCRIBED AND THAT SUBSEQUENTLY WAS NAMED FOR HIM--THE RICKETTSIA.

O A GIANT AMONG THE REMARKABLE MEMBERS OF THE STAFF WAS DR. JOSEPH GOLDBERGER. CONSIDERED TO BE ONE OF THE MOST PROMISING OF THE YOUNG MEN CONNECTED WITH THE HYGIENIC LABORATORY, IN 1914 HE WAS PLACED IN CHARGE OF THE PUBLIC HEALTH SERVICE INVESTIGATION OF PELLAGRA, THEN PREVALENT IN THE POVERTY-STRICKEN SOUTH, BUT KNOWN AS A PROBLEM IN 40 STATES.

O THE PUBLIC HEALTH SERVICE WAS DETERMINED TO MAKE AN ATTACK OF PELLAGRA, WHICH WAS THEN THOUGHT BY MEDICAL SCIENTISTS TO BE CAUSED BY AN UNKNOWN ORGANISM. DR. GOLDBERGER ARGUED THAT IF A BACILLUS WERE THE CAUSE, SOME OF THE DOCTORS AND NURSES AND OTHER PATIENT ATTENDANTS WORKING AROUND THE PELLAGRA PATIENTS DAILY WOULD GET THE DISEASE. HE POINTED OUT THAT THE ONE DIFFERENCE BETWEEN THE INMATES IN PRISONS AND MENTAL INSTITUTIONS AND THE PEOPLE WHO CARED FOR THEM, WAS THEIR DIET.

- DR. GOLDBERGER'S CONFIRMATORY INVESTIGATION WAS A CLASSIC OF EPIDEMIOLOGY. A MASTER OF BOTH OBSERVATION AND EXPERIMENTATION, GOLDBERGER SHOWED THAT THE POOR, MONOTONOUS DIETS COMMON TO MANY LOW-INCOME PEOPLE--DIETS HIGH IN CARBOHYDRATE AND LOW IN PROTEIN SOURCES AND FRESH VEGETABLES--INDUCED PELLAGRA WHEN FED TO VOLUNTEER CONVICTS IN A MISSISSIPPI PENITENTIARY. IN OTHER PUBLIC INSTITUTIONS WHERE THE DISEASE OCCURRED, INVESTIGATORS DEMONSTRATED THAT GENEROUS AMOUNTS OF MILK, EGGS, MEAT, BEANS AND PEAS PREVENTED IT. STILL, PHYSICIANS WHO WERE TREATING PELLAGRA AT THE TIME STRONGLY BELIEVED THAT IT WAS DUE TO AN INFECTIOUS ORGANISM, AND WOULD NOT ACCEPT GOLDBERGER'S EVIDENCE.

- AS FINAL PROOF THAT NO INFECTIOUS MECHANISM WAS INVOLVED, GOLDBERGER AND ONE OF HIS COLLABORATORS INJECTED EACH OTHER WITH BLOOD FROM A PELLAGRA PATIENT. LATER GOLDBERGER AND FOUR ASSOCIATES SWALLOWED CAPSULES CONTAINING PATIENTS' WASTES AND SKIN SCRAPINGS. NONE CONTRACTED THE DISEASE, ALTHOUGH IT IS NOT RECORDED WHAT ADVERSE SYMPTOMS MAY HAVE RESULTED FROM THESE HEROIC EXPERIMENTS.

- HE LATER DEVELOPED A TREATMENT USING YEAST IN THE DIET AND SHOWED THAT THE AMINO ACID TRYPTOPHAN WAS CRUCIALLY RELATED TO THE CAUSE OF THE DISEASE. SOON THE B

VITAMIN NICOTINIC ACID WAS IDENTIFIED AS A SPECIFIC PELLAGRA PREVENTATIVE, BUT UNFORTUNATELY GOLDBERGER DIED BEFORE THE GENERAL MEDICAL COMMUNITY WAS THOROUGHLY CONVINCED OF THE DISEASE'S ETIOLOGY.

- THE RANSDELL ACT OF 1930 WAS A LANDMARK IN NIH'S HISTORY. IT CHANGED THE NAME OF THE HYGIENIC LABORATORY TO THE NATIONAL INSTITUTE OF HEALTH, EXPANDING ITS EMPHASIS FROM CONCENTRATION ON INFECTIOUS DISEASES TO THE BROADER MISSION OF "ASCERTAINING THE CAUSE, PREVENTION, AND CURE OF DISEASE." IN 1938, NIH MOVED FROM THE DISTRICT OF COLUMBIA TO ITS PRESENT CAMPUS IN THE THEN, RURAL, BETHESDA, MARYLAND.

- SHORTLY THEREAFTER, WAR BROKE OUT IN EUROPE GIVING RISE TO WHAT MIGHT BE CALLED "THE MODERN NIH". FOR THE FIRST 50 YEARS OF ITS HISTORY, NIH HAD CONTINUED AS ESSENTIALLY A FREE-STANDING, INDEPENDENT LABORATORY OF LIMITED SIZE. BUT DURING THE WAR, THE MILITARY HAD LITTLE CHOICE BUT TO TURN TO ESTABLISHED NONFEDERAL LABORATORIES IN RESPONSE TO THE SUDDEN NEED FOR ADDITIONAL KNOWLEDGE TO DEAL WITH THE HEALTH PROBLEMS OF THE ARMED FORCES.

- BY GRANTS AND CONTRACTS, MOST AMERICAN SCIENTISTS NOT IN THE FEDERAL SERVICE WERE MOBILIZED FOR SUPPORT OF THE WAR EFFORT. THE ARRANGEMENT WORKED EXTREMELY WELL.

THE NEW PARTNERSHIPS GREATLY ACCELERATED BIOMEDICAL RESEARCH AND DEVELOPMENT ACROSS THE SPECTRUM FROM THE MOST BASIC STUDIES TO THE WIDESPREAD APPLICATIONS OF NEW MEANS FOR PREVENTION, DIAGNOSIS, AND TREATMENT OF DISEASE.

- BY THE END OF THE WAR THE U.S. OFFICE OF SCIENTIFIC RESEARCH AND DEVELOPMENT (OSRD) WAS ADMINISTERING A LARGE NUMBER OF MEDICALLY RELATED RESEARCH PROJECTS. A LEADING AMERICAN SCIENTIST, DR. VANNEVAR BUSH, THE PRESIDENT'S SCIENCE ADVISOR, URGED THAT THE GOVERNMENT CONTINUE TO SUPPORT THE MEDICAL RESEARCH THEN UNDERWAY IN MANY UNIVERSITIES AND HOSPITALS. AFTER DR. BUSH'S PROPOSAL WAS ACCEPTED, THE OSRD, GOING OUT OF EXISTENCE, TURNED OVER TO NIH ITS FUNDS TO BE USED AS GRANTS TO COMPLETE SOME 250 RESEARCH PROJECTS IN PROGRESS AT UNIVERSITIES, MEDICAL SCHOOLS, AND PHARMACEUTICAL COMPANIES.

- THE HIGH-LEVEL DECISION TO TRANSFER THE GRANTS TO NIH NOT ONLY CONFIRMED OUR ROLE AS THE PRINCIPAL BIOMEDICAL RESEARCH ARM OF THE FEDERAL GOVERNMENT, BUT ALSO ESTABLISHED EXTRAMURAL GRANTS AS A POWERFUL MECHANISM FOR THE SUPPORT OF SUCH RESEARCH.

- NIH HAS PROCEEDED ALONG A COURSE THAT, IN MANY WAYS,

WAS CHARTED BY A REPORT WRITTEN IN 1945 BY VANNEVAR BUSH, WHICH GREATLY INFLUENCED CONGRESSIONAL ACTION IN THE IMMEDIATELY SUCCEEDING YEARS. THIS REPORT, SCIENCE--THE ENDLESS FRONTIER, OUTLINED POLICIES FOR FEDERAL SUPPORT OF HEALTH RESEARCH THAT HAVE SERVED THE NATIONAL INTERESTS WELL SINCE THAT TIME. THE FLAVOR AND SUBSTANCE OF THE DOCUMENT STAND UP IN STURDY PERSPECTIVE WHEN VIEWED WITH THE CRITICAL HINDSIGHT OF MORE THAN 40 YEARS.

0 I WOULD LIKE TO READ A FEW KEY SENTANCES FROM IT: "THE PUBLICLY AND PRIVATELY SUPPORTED COLLEGES, UNIVERSITIES, AND RESEARCH INSTITUTES ARE THE CENTERS OF BASIC RESEARCH. THEY ARE THE WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING. AS LONG AS THEY ARE VIGOROUS AND HEALTHY AND THEIR SCIENTISTS ARE FREE TO PURSUE THE TRUTH WHEREVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE."

0 THUS, BACK IN 1945, VANNEVAR BUSH LAID THE GROUNDWORK FOR THE FEDERAL-ACADEMIC PARTNERSHIP IN THE PURSUIT OF EXCELLENCE IN SCIENCE. SUPPORT OF BIOMEDICAL SCIENCE DURING THE PAST THREE DECADES, CHIEFLY BY THE NIH, HAS TRANSFORMED OUR KNOWLEDGE AND UNDERSTANDING OF BIOLOGY. THE TRANSFORMATION HAS BEEN SO DRAMATIC, SO PERVASIVE THAT IT JUSTIFIES THE OVERWORKED TERM "REVOLUTION". NEVER IN THE HISTORY OF BIOLOGICAL SCIENCE HAS THERE

BEEN SO MUCH EXCITING WORK GOING ON, SO MANY PROMISING LEADS IN SO MANY FIELDS, OR SUCH AN ARMY OF BRILLIANT SCIENTISTS AT WORK.

- MOLECULAR BIOLOGY, WHICH BEGAN IN THE 1950S AS AN EXHILARATING INTELLECTUAL ADVENTURE IN BACTERIAL GENETICS, WITH NO PREDICTABLE PUBLIC BENEFIT, NOW PERMEATES ALL BRANCHES OF BIOLOGICAL SCIENCE. THE DISCOVERY OF ONCOGENES HAS PROVIDED A NEW PARADIGM FOR CANCER RESEARCH. IN IMMUNOLOGY, THE ONCE OBSCURE FLOCCULATIONS AND PRECIPITATIONS OF TEST TUBE SCIENTISTS HAVE GIVEN US NEW INSIGHT INTO A RANGE OF HUMAN DISEASES, NOT THE LEAST OF WHICH IS AIDS. THE NEUROSCIENCES AND GENETICS HAVE RECENTLY GIVEN US NEW HOPE AGAINST SOME OF THE MOST DEVASTATING HUMAN DISEASES--ALZHEIMER'S DISEASE, HUNTINGTON'S DISEASE, AND PARKINSON'S DISEASE. THE FIELDS OF COMPUTER SCIENCE, THEORETICAL CHEMISTRY, AND X-RAY CRYSTALLOGRAPHY, ARE COMING TOGETHER TO PROVIDE US WITH WHOLLY NEW CONCEPTS IN DESIGNING DRUGS.

- THESE ARE IMPRESSIVE EXAMPLES OF THE SUCCESSES OF THE NIH-ACADEMIA PARTNERSHIP AS ASSESSED AT THE END OF OUR FIRST CENTURY.

- BUT WHAT OF THE SECOND CENTURY OF SCIENCE FOR HEALTH?

WHAT OF THE NEW FRONTIERS? FEW, INCLUDING MYSELF, WOULD CHANCE TO SPECULATE BEYOND THE NEXT SEVERAL YEARS WHERE BIOMEDICAL SCIENCE WILL LEAD US, FOR IT IS IN THE ESSENCE OF SCIENCE THAT IT TAKES US WHERE WE'VE NEVER BEEN BEFORE AND CAN HARDLY IMAGINE.

0 THE CHALLENGE IS NOT TO PREDICT THE NEW FRONTIERS, BUT TO SET POLICY TO ASSURE THAT THE MOMENTUM OF SCIENTIFIC DISCOVERY IS MAINTAINED INTO THE NEXT CENTURY. WHATEVER THE BUDGET MAY DICTATE IN TERMS OF SCIENTIFIC OPPORTUNITIES AND PRIORITIES, THERE ARE CERTAIN ABIDING PRINCIPLES THAT AT LEAST IN THE FORESEEABLE FUTURE WILL GUIDE OUR DECISIONS.

0 ONE IS OUR CONTINUED RELIANCE UPON OUR PARTNERS IN RESEARCH--THE ACADEMIC INSTITUTIONS. DURING MOST OF THE HISTORY OF THE NIH, CERTAINLY FOR THE LAST 10-15 YEARS, ABOUT FOUR-FIFTHS OF THE AGENCY'S BUDGET HAS BEEN EXPENDED IN GRANTS AND CONTRACTS AWARDED TO OTHER INSTITUTIONS FOR THE SUPPORT OF RESEARCH. WE SUPPORT SCIENTISTS AT INSTITUTIONS SUCH AS YALE AND THE UNIVERSITY OF CONNECTICUT FOR THE COMPELLING REASON THAT YOU HAVE A NATIONAL RESOURCE FOR WHICH THERE IS NO SUBSTITUTE--YOUR FACULTIES OF TRAINED SCIENTISTS. AND FURTHER, ONE OF YOUR CENTRAL PURPOSES IS TO ENSURE THE

CONTINUING RENEWAL OF THAT PRECIOUS RESOURCE--THE TRAINED INVESTIGATOR.

- ANOTHER IS THAT THE PURSUIT OF BASIC KNOWLEDGE IS THE FOUNDATION OF ALL PROGRESS IN THE HEALTH SCIENCES. THIS IS CLEARLY SEEN IN THE CASE OF AIDS WHERE OUR TREMENDOUS ADVANCES OF THE PAST FEW YEARS HAVE BEEN POSSIBLE ONLY BECAUSE OF MANY YEARS OF BASIC RESEARCH IN IMMUNOLOGY, VIROLOGY, MOLECULAR BIOLOGY, AND MICROBIAL GENETICS. ANY RELAXATION OF THAT NECESSARILY LONG-TERM OBJECTIVE IN FAVOR OF SHORT-TERM ADVANTAGE IS A THREAT TO THE EVENTUAL TRIUMPH OVER DISEASE AND SUFFERING.

- TIED TO THE EMPHASIS ON SUPPORT OF BASIC RESEARCH IS OUR CONTINUED RELIANCE UPON INVESTIGATOR-INITIATED RESEARCH. THIS TYPE OF RESEARCH HOLDS THE GREATEST PROMISE OF SIGNIFICANT DISCOVERY AT THE FRONTIERS OF SCIENCE.

- GIVE EXAMPLE OF ZASLOFF'S WORK WHICH, ALTHOUGH IT WAS INTRAMURAL, SERVES AS A EXAMPLE OF WHAT IS SURELY GOING ON WITH OUR R01 GRANTEES EVERYWHERE. IT WAS ESPECIALLY IMPORTANT THAT THE MEDIA, AND THE PUBLIC, SEEMS TO HAVE BEEN EXCITED BY ZASLOFF'S "SERENDIPITY", PERHAPS SHOWING A CERTAIN SOPHISTICATION IN UNDERSTANDING THE IMPORTANCE OF SUPPORTING BASIC SCIENCE.

- To underline this point, I would like to close with this thought about the frontiers of science: Vannevar Bush has said, "Scientific progress results from the free play of free intellects working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown." It is on this philosophical foundation that the research support programs of the NIH were established and have continued to flourish.

REMARKS*

by

James B. Wyngaarden, M.D.**

During the past 11 months groups have met in almost every state in the Nation and in many parts of the world to pay tribute to the National Institutes of Health. The centennial observances have taken many forms, including formal symposia, dinners, lectures, exhibits, and even personal greetings from heads of state.

As far as I know, this is the first centennial picnic--and it is only appropriate that it be a gathering of the NIH family. And speaking of firsts, it is also the first time that the members of the entire NIH community, all its bureaus, institutes and divisions have joined in a festivity of this sort. We are acting out--in a way--a suggestion made by Dr. Lewis Thomas, one of America's most gifted spokesmen for medicine and science. In a foreword to a book about NIH, Dr. Thomas wrote that "the NIH laboratories are something for the Government to boast about, to dine out on and to be immensely proud of."

Indeed, we are immensely proud of the NIH and today we are, in fact, dining out in recognition of its hundredth birthday.

Who has a better right to celebrate than the personnel of NIH, and today we celebrate on behalf of all NIH personnel past and present.

In its early years the NIH family was small--not reaching a total of 100 until our 34th year in 1920, and the total was less than 200 through the agency's 50th year. It was then that NIH began to grow, reaching 1,000 by 1939, 5,000 in 1955, and 10,000 in 1961.

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*Presented at NIH Employees Recognition Day in connection with the NIH Centennial, September 11, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

Today there are more than 60 times as many NIH personnel as there were when we moved to Bethesda, but the individual's importance is as great as ever. That is why we each can take satisfaction and pride for the part we can play in this great center dedicated to better life for all.

I wish to express special thanks from all of us to the planning committee and to the many volunteers for making this day a way of saying to NIH:

Happy Birthday--and may there be many more!

Introduction for Congressman Morella

It is now my pleasure to introduce Congresswoman Connie Morella. She was elected to the 100th Congress as Representative of Maryland's 8th District, which includes the NIH. She and her husband, Tony, have lived in Montgomery County for over 32 years. They count as friends many of the NIH employees who are being recognized today.

REMARKS*

by

James B. Wyngaarden, M.D.**

Personally and on behalf of my NIH colleagues, I wish to express our deep appreciation to Dr. Tapley, Dr. Friedlander, and all our friends in the Associated Medical Schools of New York for constituting the New York Planning Committee for an observance of the NIH Centennial. We are also pleased that the New York Academy of Medicine and Rockefeller University have joined their efforts with the medical schools in planning the outstanding events that have been scheduled for the day. Our thanks to Frank Jones and the others who have devoted their efforts to making the occasion memorable.

This is a special moment in the centennial year, for it takes us to the site where the NIH began just a few days more than a hundred years ago. It is a time for briefly reviewing some of the history of that time and of the unique agency that grew from its beginnings at this place.

Two series of events--one set driven by fear of a cholera epidemic and the other by bureaucratic rivalry--converged when the Laboratory of Hygiene was established here in August 1887.

The cholera-related part of the story is concisely told by a century-old cartoon and a modern caption for it that appeared in a recent book on cholera. The cartoon was from the August 2, 1883 issue of the original LIFE magazine. In the foreground of the drawing, a Roman soldier, labeled "science," sat sleeping at his guard post, a dock at the New York waterfront. Looming over the guard, and about to pounce was a cloudy spectre, labeled "cholera," arising from a distant city across the ocean. The caption for the cartoon was from the August 2, 1883, issue of the original LIFE magazine.

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*Presented at the Associated Medical Schools of New York celebration of the NIH Centennial, Staten Island, N.Y., September 15, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

contains a rich nugget of NIH history. The authors explained, "American medical science did not slumber in 1883, it hardly existed." They added, "The concern in America about importation of cholera....sent young Dr. Joseph Kinyoun to study with Koch and Pasteur in Europe. Returning, he set up a bacteriological laboratory in the Marine Hospital, Staten Island, N.Y., in 1887." The authors then noted that "the present National Institutes of Health is directly traceable to that laboratory."

The other stream of institutional history was considerably more complicated. In truth, the establishment of a research laboratory was only an incidental issue in a struggle between two strong and determined leaders. Largely because of the cholera and yellow fever epidemics, they believed that the time had come for a national health service, but they differed on how it should be organized. One of these men, Dr. John Woodworth, was the Supervising Surgeon General of the Marine Hospital Service. He saw the new national health service as an enlarged Marine Hospital Service. He was opposed by his one-time colleague Dr. John Shaw Billings, who promoted the creation of a new National Board of Health designed to work closely with state and municipal boards of health. After an unusually bitter fight, the National Board was created in March 1879 and was given responsibility for major functions of the Marine Hospital Service. But the legislation was not a total victory for the Board. Supporters of the Marine Hospital Service are said to have had a part in influencing the Congress to add a final sentence to the bill--it read, "This act shall not continue in force for a longer period than four years from the date of its approval." This sunset provision seemed to serve, however, as a stimulus for Dr. Billings and the Board, who embarked at once full speed ahead. One of their projects was to build a ship.

It had been noted that yellow fever appeared to come into this country on infected ships in the summer and that it died out after the first frost. Dr. Billings became convinced that a refrigeration ship should be constructed for the National Board of Health. The theory was that the vessel could be used to treat incoming ships infected with yellow fever by chilling the cargo and the clothing of crew and passengers, thus killing whatever it was that was causing yellow fever. In April of 1879 the Congress passed an Act

authorizing the Secretary of the Treasury to contract for the construction of the ship and appropriated $200,000 for the purpose.

The Treasury Secretary turned the task of contracting for the ship over to Dr. John B. Hamilton, the Surgeon General of the Marine Hospital Service, who was continuing his predecessor's struggle against the Board of Health. It is not surprising that under his skillful guidance the process became impossibly complex, and that the ship sank slowly in the tides of paperwork, never to be seen again.

Undaunted by the results of the naval engagement and the expiration of the Board's legislative charter, its friends lobbied for legislation that would create a Bureau of Health in the Department of the Interior. Under the proposal the Bureau was mandated to conduct research, and to carry out all of the public health functions of the Marine Hospital Service except seaport quarantine. The bill appeared to be moving smoothly through the House when Surgeon General Hamilton appeared before the House Committee on Commerce in early 1888 to oppose the Bureau. He testified that the Marine Hospital Service was already doing all that the proposed Bureau of Health would be authorized to do. He was asked, "But what about research?" In response Dr. Hamilton revealed that during August of 1887 Dr. Joseph Kinyoun had established a small bacteriological laboratory in one of the rooms of the main hospital building on Staten Island, and that several hundred dollars had been spent on equipping the laboratory.

This was the first time a committee of Congress had heard of the Laboratory of Hygiene. It was also the end of the line for the Bureau of Health.

The Laboratory was moved to the Butler Mansion on Capitol Hill in Washington in 1891 and began to be called the Hygienic Laboratory. Congress is said to have made frequent use of the bacteriological laboratory that had been set up so close by. On one occasion Dr. Kinyoun was asked to report on the ventilation of the House of Representatives. He found illuminating gas in the air due to leaky gas pipes. He also found the air further vitiated by tobacco smoke.

The Capitol Hill site was soon regarded as too cramped. In 1902 legislation was passed providing for construction of suitable facilities designed for the laboratories. The location was near the present site of the Kennedy Center, and for the following 35 years the agency remained there.

Among the scientists associated with the Hygienic Laboratory were some of the heroes of medicine. For example, Howard Taylor Ricketts, whose work on Rocky Mountain spotted fever provided the key for finding the cause of epidemic typhus. Ricketts died of typhus in 1910, a victim of the organism he had earlier described and that subsequently was named for him--the rickettsia.

Another of the remarkable members of the staff was Dr. Joseph Goldberger. He was placed in charge of the Public Health Service investigation of pellagra, then prevalent in the South, but a problem throughout the Nation. Most medical scientists of the time thought pellagra was caused by a particular organism, but Dr. Goldberger disagreed. In time he was able to demonstrate conclusively that pellagra was caused by a dietary deficiency, and to develop effective means for prevention and cure of the disease.

In 1930, the Ransdell Act was passed changing the name of the Hygienic Laboratory to the National Institute of Health and expanding the scope of its mission from its former concentration on infectious diseases (or what were thought to be infectious) to the broader charge of "....ascertaining the cause, prevention and cure of disease."

A crucial change, creating the "modern NIH," took place at the end of World War II when the wartime Office of Scientific Research and Development (OSRD), then going out of existence, turned over to the NIH responsibility for the completion of some 250 wartime medical research projects then underway at universities, medical schools, hospitals and pharmaceutical laboratories. This high-level decision to transfer administration of the grants to NIH not only confirmed the agency's role as the principal biomedical research arm of the Federal Government, it also established extramural grants as the dominant mechanism for the support of such research.

The transfer of the funds from the OSRD involved less than $1 million and 250 grants, but the event marked the beginning of the modern NIH that funds some 28,000 projects at 1600 institutions involving some 50,000 scientists. Well over 80 percent of our current budget of $6.18 billion is expended for research and training grants and contracts.

The rapid expansion of the NIH has mirrored public concern about specific diseases and general categories of health problems. The names of the 12 institutes constitute a kind of historical catalog of problems about which there has been national anxiety. From the beginning, however, as early as the first investigations by Joseph Kinyoun at this location, NIH has placed strong emphasis on basic research.

Historians of science will probably say that the most significant contribution of the NIH thus far has been the conduct and support of pioneering work in molecular biology that began to flower in the 1950s and continues unabated. This research has led to a virtual revolution extending across all biological sciences. It is the foundation for the recombinant DNA technique, whose possibilities are only beginning to be realized. An entirely new biotechnology industry is based on the recombinant DNA discoveries.

Years of research effort and the investment of millions of dollars in basic research in such areas as virology and immunology provided a firm foundation from which to launch the massive research effort now underway against AIDS. The findings from the many studies that took place before AIDS was known to exist have greatly shortened the time required to reach our present state of knowledge about the disease and how to deal with it.

Not only have the resources of knowledge gained in other searches proved to be of great value in the fight against AIDS, it seems sure that the lessons learned in AIDS research will in turn open new doors for progress against yet other diseases. It is useful to remember that it was from an all-out effort against cholera and yellow fever a century ago that the Laboratory of Hygiene was established.

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In a taped interview for use in an NIH centennial presentation, scientist and author Lewis Thomas touched on the past and present in his apt way, and I will use his words in closing. "I think the general public is aware of the fact that we are in the early stages of a genuine revolution in biological science," he said. "The effects that this revolution is now having and will have in the years ahead on medicine are simply incalculable. All of this had its beginnings at NIH, starting around 40 years ago. All by itself this magnificent institution stands as the most brilliant social invention of the 20th century anywhere."[1]

REFERENCE

[1]Lewis Thomas, from a taped interview at Memorial Sloan Kettering Cancer Center New York, 1985.

DRAFT

FOR RELEASE UPON DELIVERY

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT

OF THE SENATE COMMITTEE ON

ENERGY AND NATURAL RESOURCES

SEPTEMBER 17, 1987

STATEMENT OF JAMES B. WYNGAARDEN, M.D.
DIRECTOR, NATIONAL INSTITUTES OF HEALTH
BEFORE THE
SUBCOMMITTEE ON RESEARCH AND DEVELOPMENT
OF THE SENATE COMMITTEE ON
ENERGY AND NATURAL RESOURCES

Mr. Chairman and Members of the Subcommittee:

I am pleased to have this opportunity to tell you about the activities of the National Institutes of Health in mapping the human genome. The National Institutes of Health (NIH) is the preeminent biomedical research organization in the world. This year, NIH is celebrating its centennial with a reaffirmation of its commitment to research, both basic and clinical, research that is dedicated to the improvement of the health of the American people by furthering the diagnosis, treatment and prevention of disease.

Genetics, the science of inheritance, has been a primary research area of the NIH for a large portion of the entire 100 years of its existence.

As you are well aware, we are currently in the midst of an explosion of biological knowledge. This greatly accelerated pace of discovery really started when the genetic material, called deoxyribonucleic acid (DNA) was found, in 1953, to have a double-stranded twisted structure called a double helix in which opposite strands were precisely joined. Inherent in this structure was the basis for passage of genetic information from one generation to the next. For this discovery, Dr. James Watson, an American, along with his British colleague, Dr. Francis Crick, were awarded the Nobel Prize.

Since then, discovery after discovery in the area of genetics have come so rapidly that the term "biological revolution" is often used. Almost all these new findings have come from American scientists supported by NIH. Six

additional Nobel prizes have been awarded for work on DNA structure--all to NIH-funded scientists. The Congress of the United States has recognized the importance of such research to the well-being and improved health of the American people and has consistently supported the NIH budget for this work.

The current budget for NIH is $6.2 billion of which about $2 billion is in an area called biotechnology. About one-half of this amount, or $1 billion, is devoted to genetics, DNA research, and the related service base. This field has developed rapidly, as a result of the discovery of a technique known as recombinant DNA technology which permits the snipping of a small piece of DNA from one site in the gene, and its insertion into another--even into the DNA of another different organism, if that is desired. Again this discovery was made by American scientists who also won the Nobel Prize. The use of this technology has not only spawned the new biotechnology industry, able to produce important chemicals and drugs, but has also made it possible to do the project which S. 1480 proposes, to map and eventually to sequence the entire human genome, the complete genetic material of man. The project is actually feasible now, and with further methodological advances will be easier and cheaper in the future.

NIH has long been committed to the support of research leading to a full understanding of the genetics of normal human development and of what goes wrong in human disorders. This work is absolutely indispensable to our mission of acquiring a deep understanding of how biological systems develop and function, and what goes awry in the thousands of diseases that affect mankind. Molecular biology and molecular chemistry are the central themes, the pervasive mechanisms of most of what our scientists do.

In Fiscal Year 1986, NIH provided $300 million of its funds to about 3,000 research projects related to the elucidation of complex genomes, of which about $100 million was related to mapping and sequencing the human genome. Scientists supported by NIH are now engaged in a concerted effort to "map" or pinpoint the specific location of genes on chromosomes, especially those genes responsible for inherited disorders. Researchers have already mapped many genes and have found the approximate locations of the genes for Huntington's disease, Duchenne's muscular dystrophy, retinoblastoma (cancer of the eye in children), some forms of manic-depressive illness, cystic fibrosis, cancer of the colon, and Alzheimer's disease, as well as a number of other disorders. Finding these genes will allow researchers to make copies of them for study, to learn what protein each gene makes, to define the precise mechanism of causation of these disorders, to understand ways to treat disorders that arise from defects in these proteins, and perhaps even to replace defective genes. However, mapping genes on the chromosomes of complex organisms and determining the order or sequence in which the chemical units of DNA are arranged represent major challenges, challenges that NIH is prepared to undertake now in coordination with the other Federal agencies represented here today, as well as with the university community and the biotechnology industry.

NIH believes the National Laboratories can play a very substantial role in the program to map the human genome, particularly the Los Alamos National Laboratory. Indeed, it already does so. Let me explain:

It became clear, some time ago, that an organized effort was needed to store, catalog, and distribute the nucleic acid sequence data that were being generated so rapidly. In 1979, Dr. Walter Goad of Los Alamos National Laboratory began a DNA sequence data base as a pilot project. Subsequently,

based on his success, NIH established GenBank in 1982. This data base is still developed and prepared for distribution by scientists at the Los Alamos National Laboratory. During the first five years of the contract, $3.6 million has been spent for this effort. During this time, the number of nucleic acid sequences appearing in the literature has increased tenfold and, as efforts to map and sequence the human genome are intensified, the data will multiply very rapidly. We anticipate a possible increase of 16 times the number of sequences determined per year. NIH will soon award the new GenBank contract and provisions for these increased needs have been made.

In order to assure that all these efforts to characterize the human genome (by that I mean to map and then to sequence) are complementary to each other, the NIH of the Department of Health and Human Services (DHHS); the Office of Health and Environmental Research (OHER), Department of Energy (DOE); and the Biological, Behavioral, and Social Sciences Directorate (BBS), of the National Science Foundation (NSF); have implemented a coordinated effort. Currently, there is a group known as the Biotechnology Working Group of the Domestic Policy Council. A subcommittee of this group has been established. In addition to NIH, OHER, and the NSF, the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the United States Department of Agriculture (USDA) are represented. I serve as the Chairman of this subcommittee. In this role, I intend to assure that the project to characterize the human genome is carried out by the scientific organizations most qualified to do the work, is a coordinated effort, and that there is no unnecessary duplication of effort. The scientific and technical skills of researchers throughout the country in Federal, university, and industrial laboratories, as well as at the National Laboratories, must and will be

utilized to the maximum, thus assuring that the U.S. continues to retain its competitive edge worldwide in genetics research and biotechnology.

Characterizing the genomes of a number of complex organisms is a natural outgrowth of all our efforts directed toward understanding biology. The limitations are resources--not coordination. Eventually, technological and methodological improvements will enhance efficiency and reduce the costs of genetic mapping and sequencing. Within the year, two major reports will be published, one by the National Academy of Sciences, and the second by the Office of Technology Assessment. Both of these documents will provide a comprehensive overview of the state-of-the-science and the cost of reaching the next level of technological achievement. At NIH, we are already expanding our activities in genomic analysis, and other organizations have similar plans. The Domestic Policy Council Subcommittee on the Human Genome provides a productive channel for sharing our research results, for establishing collaborative projects, and for coordinating future plans.

While we agree with the intent of S. 1480 to highlight the importance of understanding the genetic basis of living organisms, we do not feel that the bill describes the optimal route toward attaining these objectives.

Mr. Chairman, members of the subcommittee, this concludes my prepared remarks. I would be pleased to answer any questions you would like to ask.

DRAFT

OPENING REMARKS AND HISTORY OF NIH*

By

JAMES B. WYNGAARDEN**

Some of you already know the simple version of the origins of the National Institutes of Health--from the one-room attic laboratory on Staten Island set up to investigate cholera and other infectious diseases to the $6.2 billion enterprise of today. But, as I have learned in my five years in the Washington milieu, nothing is simple when you have a national emergency (as cholera, yellow fever, influenza), several competing agencies, a concerned Congress, and several strong personalities. In addition to their battles against disease, the founding scientists --back in the 1880s-- were engaged in a fierce bureaucratic struggle.

The two prinicipal contestants were our organizational ancestor, the Marine Hospital Service, and the then newly created National Board of Health. This decisive battle was

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*Presentation at Duke University Celebration of the NIH Centennial, Durham, North Carolina, September 21, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

joined over the construction of a refrigerator ship, but the basic issue was not supremacy of the seas but the more familiar contest for bureaucratic turf. As it turned out, this time of troubles became the birth pains of the NIH.

The National Board of Health was created by the Congress in 1879. The legislation creating the new body called upon the board to frame all rules and regulations to prevent the introduction of contagious diseases into the United States, to gather information on all matters affecting public health, to give advice on the subject to the federal government and the states, and to prepare a plan for a permanent national public health organization. It proposed as one of its first moves to take from the Marine Hospital Service authority over the newly passed quarantine law.

The urgent attention given to this matter by the Congress reflected public alarm over the yellow fever epidemic of 1878. That fear provided powerful motivation for any action that appeared to have promise. Because yellow fever apparently came into this country on infected ships in the summer and died out with the autumn cold, the National Board of Health became convinced that a refrigerator ship could be used to treat incoming cargo as well as the clothing of crews and passengers, thus killing whatever it was that caused the disease. Within weeks, the Congress appropriated $200,000 to be used by the Secretary of the Treasury for the

construction of the ship and provided that the plans were to be approved by the National Board of Health.

Meanwhile, the nascent NIH--the Marine Hospital Service --was not particularly enthusiastic about the project or, for that matter, with any of the threatening activities of the Board. In a short time, however, the Board's plans for the refrigerator ship were completed and submitted to the Secretary of the Treasury.

But the Secretary of the Treasury referred the Board's plans to his principal health advisor, John B. Hamilton, who was also the supervisory Surgeon General of the Marine Hospital Service. Yes, strange at it may seem, in that period, the antecedent NIH served under the flag of the Department of the Treasury! To make a long story short, the plans for the refrigerator ship sank slowly from sight under the waves of paper whipped up by the Treasury Secretary with the advice of the Surgeon General.

The battle raged on, however, for almost a decade. One last, fullscale attack was made on the Marine Hospital Service in 1888. Friends of the now defunct National Board of Health had successfully lobbied commmittee approval of a bill to set up a Bureau of Health in the Department of the Interior, stripping the Marine Hospital Service of all of its public health functions but quarantine. Even after the

committee had voted to report favorably on the bill, Surgeon General Hamilton asked to appear before the committee to oppose the measure. On February 24, 1888, he testified that the Marine Hospital Service was already doing all that the proposed Bureau of Health would be authorized to do.

"But how about research?" the Committee asked.

And Hamilton played his trump card, which probably saved his Service.

The Surgeon General's ace was his testimony that the Service had already begun to conduct medical research in a small laboratory on Staten Island--and that $300 had been spent on the latest Zeiss microscopes. He revealed that, only a few weeks before, research reports had been published on the work being carried out in the laboratory by an officer in the service, Dr. Joseph J. Kinyoun, who was head of the research facility.

This was the first time a committee of Congress had heard of the National Laboratory of Hygiene, which eventually would become the National Institutes of Health.

At that time, medical science in the United States lagged far behind that in Europe. The new discipline, bacteriology,

led by Pasteur and Koch, was involving more and more European laboratory workers, but few Americans had participated in that advance. The new National Laboratory of Hygiene was in effect a fragile transplant from Europe, for Dr. Kinyoun had studied with Koch as well as at the Pasteur Institute in Paris.

In just a few years, in 1891, that fragile transplant was moved to Washington, D.C. firmly underscoring the laboratory as a National resource. Here--first at a location near the Capitol and then at a location near the present Kennedy Center-- the laboratory was the site of many heroic and successful battles against disease.

Among the scientists associated with the Hygienic Laboratory were some of medicine's heroes. For example, Dr. Howard Taylor Ricketts, whose work on Rocky Mountain spotted fever provided the key for finding the cause of one of the great plagues of mankind--epidemic typhus. Ricketts died of typhus in 1910, a victim of the organism that he had earlier described and that subsequently was named for him--the Rickettsia.

Two years later, in 1912, Dr. T. B. McClintock was sent from the Hygienic Laboratory to Montana to carry out a project that had been planned by Dr. Ricketts. He completed the

project, but in the process contracted spotted fever and died shortly after returning to Washington. Another medical hero.

A giant among the remarkable members of the staff was Dr. Joseph Goldberger. Considered to be one of the most promising of the young men connected with the Hygienic Laboratory, he was placed in charge of the Public Health Service investigation of pellagra, then prevalent in the South, but known as a problem in 40 states as well as the District of Columbia. Goldberger's story may be of special interest to this audience because this region also played a role in the ultimate solution to the mystery of pellagra.

The disease was then thought by most medical scientists to be caused by a particular organism. Dr. Goldberger argued that if a bacillus were the cause, some of the doctors and nurses and other attendants working around the pellagra patients would get it. He pointed out that the one difference between the inmates in prisons and mental institutions, and the people who cared for them, was their diet. Many of the inmates suffered from pellagra, whereas their attendants did not.

Dr. Goldberger's confirmatory investigation was a classic of epidemiology. A master of both observation and experimentation, Goldberger showed that the poor, monotonous

diets common to many low-income people--diets high in carbohydrate and low in protein sources and fresh vegetables--induced pellagra when fed to volunteer convicts in a Mississippi penitentiary. In other public institutions where the disease occurred, invesigators demonstrated that generous amounts of milk, eggs, meat, beans, and peas prevented it. Still, physicians who were treating pellagra at the time strongly believed that it was due to an infectious organism and would not accept Goldberger's evidence.

As a final proof that no infectious mechanism was involved, Goldberger and one of his collaborators injected each other with blood from a pellagra patient. Later, Goldberger and four associates swallowed capsules containing patients' wastes and skin scrapings, and Goldberger injected blood from a pellagrous woman into his wife, Mary. None contracted the disease, although it is not recorded what adverse symptoms may have resulted from these heroic experiments.

use slide of letter to W. W.Rankin from Goldsboro State Hospital in NC.

He later developed a treatment using yeast in the diet and showed that the amino acid tryptophan was crucially related to the cause of the disease. At the time of his death in

1929, Dr. Goldberger had established that there was something that he called pellagra-preventive factor, that was probably a vitamin, but he had not isolated that factor. He knew which foods contained the factor and had developed lists of the foods for use in prescribing for people so as to prevent the disease. He kept adding to these lists until be was no longer able to work. About this time, a host of scientists were linked in close competition for the isolation of nicotinic acid as the pellagra-preventive factor, including .....(Dr. Wyngaarden to fill in this part.)

The Ransdell Act of 1930 was a landmark in NIH history--even in the institutional history of biomedicine. It changed the name of the Hygienic Laboratory to the National Institute of Health, expanding its emphasis from concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention and cure of disease."

In 1938, NIH moved from its D.C. location to its present campus which soon included six buildings. Then, a year later, war began in Europe.

(FDR slides and tape) Full length is 10 minutes starting at Marine Band.

In 1940, FDR dedicated the first several buildings on the NIH campus, standing on the portico of Building 1, now called the James A. Shannon Building. This tape, taken from a wire recording, gives a sense of those times and seems remarkably timely even today.

The ascendency of the modern NIH to its present position of world leadership in biomedical science can be traced to the changes brought by World War II, to the uprooting of European culture, and the cooperative relationships forged out of wartime necessity between the U.S. government and academia.

To meet the urgent health needs of the armed services, the Government turned to the established non-federal laboratories for help in conducting vital research. Grants and contracts were awarded for the support of such essential investigations. This arrangment worked exceedingly well. These newly formed partnerships greatly accelerated progress in research and development across the spectrum, from the most basic research to studies on the widespread application of newly formulated measures for prevention, diagnosis, and treatment of disease.

By the end of the war the U.S. Office of Scientific Research and Development (OSRD) was administering a large number of medically related research projects. A leading American

scientist, Dr. Vannevar Bush, the President's science advisor, urged that the government continue to support the medical research then underway in many universities and hospitals. After Dr. Bush's proposal was accepted, the OSRD, going out of existence, turned over to NIH its funds to be used as grants to complete some 250 research projects in progress at universities, medical schools, and pharmaceutical companies.

The high-level decision to transfer the grants to NIH not only confirmed our role as the principal biomedical research arm of the Federal Government, but it also established extramural grants as a powerful mechanism for the support of such research.

NIH has proceeded along a course that, in many ways, was charted by a report written by Vannevar Bush, which greatly influenced congressional action in the immediately succeeding years. This report, Science--the Endless Frontier--outlined policies for federal support of health research that have served the national interests well since that time. The flavor and substance of the document stand up in sturdy perspective when viewed with the critical hindsight of more than 40 years. I would like to read a few key sentences from it:

"The publicly and privately supported colleges, universities, and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge."

Thus, back in 1945, Vannevar Bush laid the groundwork for the Federal government-academic partnership in the pursuit of excellence in science. Support of biomedical science during the past three decades, chiefly by the NIH, has transformed our knowledge and understanding of biology. The transformation has been so dramatic, so pervasive that it justifies the overworked term "revolution." Never in the history of biological science has there been so much exciting work going on, so many promising leads in so many fields, or such an army of brilliant scientists at work.

Molecular biology, which began in the 1950s as an exhilarating intellectual adventure in bacterial genetics, with no predictable public benefit, now permeates all branches of biological science. Human insulin, interferons, human growth hormone are being produced by bacteria. The discovery of oncogenes has provided a new paradigm for cancer research.

In immunology, the once obscure flocculations and precipitations of test tube scientists have given us a wholly new insight into a range of human diseases and, in the instance of monoclonal antibodies, provides us a tool whose power is yet to be fully exploited in terms of targeted chemotherapy and even fertility control. These are impressive examples of the successes of the NIH-academia partnership as assessed at the end of our first century.

But what of the second century of science for health? Few, including myself, would chance to speculate beyond the next several years about where biomedical science will lead us, for it is the essence of science that it takes us where we've never been before and can hardly imagine.

The key question is how shall we--in terms of policy--make sure that the momentum of scientific discovery is maintained into the next century? Whatever the budget may dictate in terms of scientific opportunities and priorities, there are certain abiding principles that at least in the foreseeable future, will guide our decisions.

One is that the pursuit of basic knowledge is the foundation of all progress in the health sciences. This is clearly seen in the case of AIDS where our tremendous advances of the past few years have been possible only because of many years of support for basic research in immunology, virology,

molecular biology, and microbial genetics. We must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over disease and suffering.

Another guiding principal is reliance upon our partners in research--the academic institutions. During most of the history of the NIH, certainly for the last 10-15 years, about four-fifths of the agency's budget has been expended in grants and contracts awarded to other institutions for the support of research. We support scientists in such institutions as Duke for the compelling reason that you have a national resource for which there is no substitute--your faculties of trained scientists. And further, one of your central purposes is to ensure the continuing renewal of that precious resource--the trained investigator.

A third fundamental principal guiding the NIH is that investigator-initiated research into biological processes holds the greatest promise of signficant discovery. Through competing research projects, we tap the best minds for the most creative ideas, weigh them through peer review of substance and methodology, and test them through challenge and open exchange of information.

A fourth principle is the need to assure a continuing supply of well-trained scientists to carry out the research to meet national health needs. There is a close relationship between research productivity and the availability and replentishment of the supply of qualified investigators.

I would like to close with a thought from Vannevar Bush about the frontiers of science. He said: "Scientific progress results from the free play of free intellects working on subjects of their own choice, in the manner dictated by their curiosity for exploration of the unknown." It is on this philosophical foundation that the research support programs of the NIH were established and have continued to flourish.

INTRODUCTORY REMARKS*

for

James B. Wyngaarden, M.D.**

Ladies and gentlemen, welcome to the NIH Lecture. This afternoon we are honored to have as our speaker a distinguished visitor from overseas. Dr. Michael Berridge comes to us from Cambridge University, where he is senior principal scientific officer of the Unit of Insect Neurophysiology and Pharmacology.

Dr. Berridge's career has been marked by his efforts to solve a fundamental problem in cell biology. The problem is to understand the second messenger system: how cells detect external signals and translate them into the internal signals, cyclic necleotides and calcium, that produce a change in the cell's activity. Disturbances in this signal system are likely to be at the basis of a number of diseases--so it is critical that we find out how the system works normally and what can go wrong.

Until recently, an unsolved mystery was how a hormone, which attaches to a surface receptor and does not move through the cell membrane, can trigger release of calcium inside the cell. In 1975, Dr. Robert Michell proposed that substances in the cell membrane, called inositol phospholipids, might be the missing link in this process. Although the association was strong, it remained an hypothesis until 1984, when Dr. Berridge provided the experimental proof and an explanation.

In studies of cells from the salivary gland of the blowfly, he showed that inositol trisphosphate, a product of the inositol phospholipids, caused release of calcium inside the cell in response to the hormone serotonin. His finding has since been confirmed in many kinds of cells and with many other hormones. The prompt replication of his findings by other investigators, in diverse tissues from different species, was facilitated by the elegant simplicity of his experimental techniques.

After receiving his doctorate from Cambridge University in 1965, Dr. Berridge spent several years in the United States as a postdoctoral fellow and research associate. He returned to Cambridge in 1969 to become senior scientific officer of Cambridge's Unit of Invertebrate Chemistry and Physiology, and has been at the university ever since. A fellow of Cambridge's Trinity College and The Royal Society, he serves as co-editor of Advances in Insect Physiology, and is a member of the editorial boards of three other scientific journals. In 1986, his research was honored twice: he was the recipient of both the King Faisal International Prize in Science and the Louis Jeantet Prize in Medicine.

And now, it is my great pleasure to introduce our speaker, whose talk is titled "Inositol Lipids and Intracellular Communication."

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*For Dr. Michael Berridge, NIH Lecturer, on September 23, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

INTRODUCTORY REMARKS*
BY
JAMES B. WYNGAARDEN, M.D.**

I want to thank Dr.Macedo and the delegates of the member countries making up the Directing Council for the handsome plaque given to me earlier, in commemoration of the Centennial of the National Institutes of Health. It is fitting that this evening's NIH-PAHO panel is organized around the topics--yesterday's problems, today's challenges, and tomorrow's issues--because that theme captures the essence of the long-term cooperation between our two organizations and with the member countries.

I might add that commitment to international cooperation in science and public health is not just of importance to the NIH, but to the U.S. government as a whole. In fact, my very first duty as NIH Director-Designate--more than five years ago--was to represent Dr. Edward Brandt, then Assistant Secretary for Health, at a Pan American Health Organization meeting in Caracas.

International cooperation has been a hallmark of biomedical science since the late 1800s, the dawn of scientific medicine, when the new science of bacteriology opened unheard of possibilities for the prevention of disease.

In the 1880s health in other nations was of interest to the United States mostly from the viewpoint of learning what doctors and scientists elsewhere were doing to diagnose, treat, and prevent illness. It was in this spirit that the founding father of the NIH, Dr. Joseph Kinyoun, traveled to the great European laboratories of the time to learn about the new science, its methods, and tools. In 1887, in setting up the Laboratory of Hygiene, he would base his own research studies on what he had learned abroad.

This era, too, saw the beginnings of international cooperation in setting public health policies. In 1881, the United States hosted the International Sanitary Conference in Washington, D.C., when domestic legislation involving inspection of ships in their home ports demanded international consensus. Although this meeting, which drew delegates from 26 nations, yielded little--as had four previous international conferences--the U.S. continued to participate in nine subsequent meetings. These sessions prepared the way, haltingly, for the eventual formation of the World Health Organization. (From Advances in American Medicine: Essays at the Bicentennial, edited by Bowers and Purcell, published by Josiah Macy, Jr., Foundation with the NLM)

The challenge of yellow fever signalled the first direct international involvement of the United States. Many know the dramatic story of Walter Reed and the U.S. Army Yellow Fever Board in Havana, but there were other heroes who deserve credit. Among them were Carlos Finlay, a Cuban physician

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*Remarks At the Pan American Health Organization Celebration of the NIH Centennial, Washington, D.C., September 25, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

who had become convinced as early as 1880 that yellow fever is transmitted by the Aedes aegypti mosquito, and Henry Rose Carter, of the U.S. Public Health Service who--having observed an epidemic of yellow fever in Mississippi in 1898--held forth the view that there appeared to be an "extrinsic incubation period" between the time of the appearance of the first case and the occurrence of secondary cases. This collaborative success in controlling Yellow Fever in Havana during the war with Spain and in Panama during the construction of the canal, provided a new perspective on international health.

Perhaps an even greater accomplishment of this period than the control of yellow fever was the stage setting for continued international cooperation. In 1902 the U.S. joined several countries of the Western Hemisphere in forming the International Sanitary Bureau, which later would become the Pan American Health Organization in 1948. Through these early days of cooperation, other common problems were attacked: typhus, Rocky Mountain Spotted Fever, and Bolivian hemorrhagic fever, to name just a few.

Today, NIH, the Pan American Health Organization, and its member counties are united in cooperation against health problems and in scientific concerns perhaps even more challenging than those of the early years.

NIH and PAHO have enjoyed long-standing research cooperation in many areas, particularly related to improved maternal and child health and control of infectious diseases. In recent years, research cooperation has been directed to health problems corresponding to changes in demographic profiles within the region, for example, cardiovascular diseases, diabetes and digestive disorders, allergic diseases, and problems of aging. A number of these activities have been undertaken by 15 components of NIH in their role as WHO Collaborating Centers.

The newest and most urgent area of collaboration is in AIDS, a particularly challenging entity for PAHO, given the differing epidemiologic patterns of the disease in various parts of Latin America. The recent two-day international, satellite teleconference on "AIDS in Latin America" has charted the way for further cooperation.

Finally, NIH and PAHO also have mutual interests in strengthening the health infrastructure: for example, maintaining equipment and instrumentation essential to health care and research facilities; conserving and breeding primates for biomedical research and testing; improving access to library materials and other information sources. In fact, this year marks the 20th anniversary of PAHO-National Library of Medicine cooperation in running the region's Latin American biomedical library network, housed in Brazil.

In closing, I want to thank Dr. Macedo and the delegates for honoring NIH's centennial this evening and wish you an interesting and productive panel discussion, and festive reception.

TALKING POINTS

National Cancer Advisory Board Meeting

September 28, 1987

- AIDS research to be topic of November meeting of Advisory Committee to the Director.

  The next meeting of the Advisory Committee to the Director will take place on November 18-19. The meeting will address "The Role of Biomedical Research in Combating AIDS." The program has been structured to examine: the nature and extent of the biomedical research community response to this public health emergency; the administrative structure set in place to coordinate the Federal AIDS effort; the public's attitudes and concerns regarding AIDS research; and congressional actions in response to the AIDS epidemic. The meeting will also focus on the status and future direction of biomedical science in those areas that offer the greatest hope towards the eventual resolution of the AIDS epidemic.

- Regional meetings of Advisory Committee to the Director.

  A series of regional public briefing meetings will be held during the period from November 1987 through March 1988 to extend and intensify deliberations of the Advisory Committee to the Director on "The Health of Biomedical Research Institutions."

THE PURPOSES OF THE MEETINGS ARE:

1) TO PROVIDE CURRENT INFORMATION ON THE ACTIVITIES OF THE NIH BY DESCRIBING THE BROAD POLITICAL CONTEXT IN WHICH THE NIH OPERATES, DISCUSSING THE FEDERAL BUDGET PROCESS AS IT AFFECTS THE FORMULATION OF THE NIH BUDGET, DEMONSTRATING RECENT TRENDS IN THE FUNDING OF NIH PROGRAMS, DISCUSSING THE BROAD STRATEGIES ADOPTED BY THE NIH TO MEET EMERGING NEEDS, AND DESCRIBING NEW NIH POLICIES AND PROGRAMS DESIGNED TO ACHIEVE PROGRAM OBJECTIVES.

2) TO SOLICIT THROUGH PUBLIC TESTIMONY THE VIEWS OF BIOMEDICAL RESEARCHERS, UNIVERSITY FACULTY AND ADMINISTRATORS, REPRESENTATIVES OF PROFESSIONAL SOCIETIES, AND OTHER INTERESTED PARTIES CONCERNING THE IMPACT OF THE FEDERAL SYSTEM OF SPONSORED RESEARCH ON THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS.

BY FAR, A MAJOR PORTION OF THE MEETINGS WILL BE DEVOTED TO PUBLIC TESTIMONY. ACCORDINGLY, WE WILL CONVENE FOR EACH MEETING A PANEL COMPRISED OF MEMBERS OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH, REPRESENTATIVES OF NATIONAL ADVISORY COUNCILS AND BOARDS, BID DIRECTORS AND SENIOR OD STAFF TO RECEIVE THIS TESTIMONY AND INTERACT WITH PUBLIC WITNESSES.

o Allocation of beds to National Cancer Institute.

The 26 beds on the 12th floor East of the Clinical Center were allocated to the National Cancer Institute as of August 28. The reassignment of the beds on 12 East, plus the present complement of beds assigned to the Institute, returns the number of beds assigned to the National Cancer Institute to a total of 149. Within this bed space the NCI will be able to accelerate its research on drug development for AIDS while maintaining its support for inpatient cancer research and providing for short-term collaborative AIDS research with other NIH institutes.

Consideration will be given for allocating additional beds specifically for AIDS inpatient clinical research should that be necessary in the future.

COMMENTS AT THE BALTIMORE CELEBRATION
OF THE NIH CENTENNIAL*
BY
JAMES B. WYNGAARDEN M.D.**

I am very happy to be here this afternoon to join in this luncheon and symposium marking the Centennial of the National Institutes of Health. Personally and on behalf of all my NIH colleagues I wish to express my deepest appreciation to Dr. Steven Muller, President of the Johns Hopkins University and Dr. Edward Brandt, Chancellor of the University of Maryland at Baltimore, and all of those involved in the Baltimore Celebration for putting together this event. The distinguished panel of speakers you have assembled for this afternoon--a number of them with close past ties to the NIH--will address some of the most exciting areas of today's biomedical science.

I am particularly pleased that the Baltimore group has chosen to focus attention on the so-called new era of biotechnology because this will provide me with an opportunity to say a few words about the modern partnerships among government, academia, and industry and about the importance of supporting basic research. Your program for today has fulfilled our highest hopes as to how the observance of the NIH Centennial would contribute in a special way to our nation's research efforts as we enter the new century with its challenges and magnificent opportunities.

But first, I ask your indulgence as I mention a highlight or two of centennial history.

As some of you may know, the Laboratory of Hygiene, the forerunner of the National Institutes of Health, was established in 1887 on Staten Island for purely practical reasons: to help combat the major problems confronting public health officials at the time--yellow fever, cholera, and other infectious diseases believed to be entering New York harbor along with immigrants. The objective of the director, Dr. Joseph Kinyoun, was very specifically to contribute to the control of the urgent epidemics of communicable disease. Foresighted as he was, Kinyoun saw that the likely answer lay in the Laboratories of Europe where the new science of bacteriology was taking hold. This was a period when, as William Osler later wrote, "The spirit of science was brooding on the waters." As he put it, "preventive medicine was an incomplete blundering science until bacteriology opened unheard of possibilities . . . ." Once that branch of science took hold, tremendous advances were made.

Thereafter, starting with that one room laboratory on Staten Island, the Federal Government was to embrace as a national mission the support of

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*Comments at the Baltimore Celebration of the NIH Centennial, Hyatt Regency Hotel, Inner Harbor, Baltimore, Maryland, September 29, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

biomedical research. In 1891 the Laboratory was moved to Washington D.C., firmly establishing it as a national resource, and lending its expertise to the solution of a number of important health problems: among them Rocky Mountain spotted fever, pellagra, and psittacosis.

The Ransdell Act of 1930 was a landmark in NIH history. It changed the name of the Hygienic Laboratory to the National Institute of Health, expanding its concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention and cure of disease".

During this period, the operating philosophy of the new NIH became an issue. A debate began about whether the still small NIH should support research scientists whose work might not have immediate practical value in preventing and treating disease. The Surgeon General of the Public Health Service, Hugh S. Cummings, contended that such support was necessary. He had in mind the work of Dr. Claude Hudson of NIH. "I do not know of any possible connection Professor Hudson's work on sugar will have to public health," Surgeon General Cummings said to the Congress, "yet, you can never tell." Dr. Hudson's discoveries about the structure of carbohydrates later became not only a landmark in organic chemistry but essential to our knowledge of the several pathways of glucose metabolism.

Thus, NIH established early its policy of supporting research in the basic sciences while always encouraging its practical applications. Shortly thereafter, in 1938, NIH moved to its present location in Bethesda, Maryland and was renamed the National Institutes of Health.

World War II signalled the era of the "modern" NIH--the formation of strong partnerships with Johns Hopkins and the University of Maryland, and other academic institutions around the country. The high-level decision to transfer some 250 war-related medical research projects being conducted in universities and medical schools to NIH's portfolio confirmed our ongoing relationships with our academic partners in discovery.

That period also underscored our emphasis on basic research and the conviction that investigator-initiated research into biological processes holds the greatest promise of significant discovery.

Certainly, NIH can take some pride in its role in fostering the biomedical research enterprise largely centered at academic centers. A measure of the success of this endeavor--I think a key accomplishment--has been the fostering of the so called new biotechnology revolution.

This enterprise has burgeoned into a billion dollar industry that already can be credited with many advances to help mankind. Promises for the future are incalculable. These vast accomplishments and promises are to a great extent the result of steadfast support for basic biomedical research by the NIH.

For more than 30 years, NIH has funded pioneering investigations and research training in basic sciences--molecular genetics, molecular and cell biology, and immunology--to advance understanding of biological processes in health and disease. In addition, most of the men and women who today

are participating in the biotechnology drama were trained by or through the NIH.

These developments--gene manipulation, cloning of DNA, and creation of monoclonal antibodies--and recognition of their possible commercial applications, have brought a new member strongly into the biomedical research partnership: industry.

But, what of the future? What of the next century? Few, myself included, would chance to speculate beyond the next several years about where biomedical science will lead us, for it is inherent in the essence of science--particularly basic science--that it takes us where we've never been before and can hardly imagine.

Two things are certain: First, that challenges and opportunities remain to occupy the full talents of the three partners--government, academia, and industry. And second that we must continue to increase our store of fundamental knowledge. Any relaxation of that necessarily long-term objective in favor of short-term advantage is a threat to the eventual triumph over all disease and suffering.

With these closing thoughts, I would like to commend to you the talks to follow on some of the most invigorating areas of today's biomedical science.

REMARKS*

by

James B. Wyngaarden, M.D.**

During the past year some of my colleagues and I have had the pleasure of participation in a variety of dinners, seminars, at least one picnic, and other special events in many different parts of the world saluting the centennial of the National Institutes of Health. None of these events has excelled the NIH Centennial Commemorative Day Celebration in Massachusetts. I do not know how it would be possible to assemble a more distinguished panel of speakers than the ones who appeared today in the symposium on "Frontiers in the Life Sciences." Tonight's dinner reminds me of a sentence in one of Ron Lamont-Havers' letters to me when he said, "We are looking forward to September 30 as our Gala Event." And so it is.

Personally and on behalf of all my NIH colleagues I wish to express deepest appreciation to John Potts, to the subcommittee chairmen, and to the members of the Massachusetts Committee. The list of 32 member institutions is a Who's Who of America's academic, scientific and medical organizations.

The Massachusetts Committee has focused attention on the hopes and needs of biomedical research in the context of the history of the past century. They have pointed out how Massachusetts scientists have been responsible for a disproportionately large share of accomplishments in biomedical research during the hundred years, but at the same time the Committee has made known its concern about the prospects for continuing this unique tradition of achievement.

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*Presented at the Massachusetts NIH Centennial dinner, Boston, Massachusetts, September 30, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

They have stressed the importance of stable funding for biomedical research so that young scientists can feel reasonable assurance that they will be able to pursue careers in health-related research. The maintenance of our Nation's scientific leadership in this vital field does indeed depend upon a continuous infusion of well trained, highly motivated young scientists.

The Committee has also urged a renewed commitment to science education in secondary schools as an essential step toward the creation of tomorrow's generation of researchers, and further, as a means for fostering the scientific literacy our technological society demands.

Your plans and your actions have fulfilled our highest hopes as to how the observance of the NIH centennial could contribute in a special way to our Nation's research efforts as we enter the new century with its challenges and magnificent opportunities.

For a few minutes I ask your indulgence as I mention a highlight or two of centennial history.

My sense of the early history of the institution was refreshed about two weeks ago when I was privileged to unveil a plaque at the original site of the Laboratory of Hygiene on Staten Island. The ceremony was a part of the centennial observance sponsored by the Associated Medical Schools of New York.

In the course of the day we recalled together the circumstances that prompted the establishment of the Laboratory and the status of science and medicine in this country at the time the NIH came into being.

I told the group of a cartoon that was reprinted in a recent book on the "American Scientific Experience with Cholera," written by W. E. Van Heyningen and the late John R. Seal. The drawing came from the August 2, 1883, issue of the original LIFE magazine. In the foreground a Roman soldier, labeled "science," sat sleeping at his guard post, a dock on the New York waterfront. Looming over the guard was a ghastly spectre labeled

"cholera" that seemed to rise from a distant city across the ocean. The modern caption for the cartoon provides a latter-day comment on the 1880s. Referring to the sleeping sentinel, the caption asserted that, "American medical science did not slumber in 1883, it hardly existed." The authors added a nugget of NIH history by explaining further, "The concern in America about importation of the fifth cholera pandemic of 1881 sent young Dr. Joseph Kinyoun to study with Pasteur and Koch in Europe. Returning, he set up a bacteriological laboratory in the Marine Hospital, Staten Island, New York, in 1887."[1] And as we all know, the present National Institutes of Health is directly traceable to that laboratory.

Dr. Kinyoun quickly made known to the U.S. Congress and the American people the importance of what was taking place in medical science in Europe and its relevance to his goals for the new laboratory. He stated to the Congress that, "....this laboratory, situated and equipped as it is, should form the nucleus of one national in its character, and developed on the same line as those established in Germany, France and England."[2]

The first steps toward realization of Dr. Kinyoun's goal to make the laboratory a national resource were taken when the modest laboratory was moved in 1891 to temporary quarters in Washington. By 1904 the laboratory had been settled in newly constructed buildings in downtown Washington, where it remained for 35 years. During this period and up until the end of World War II, the NIH was a freestanding Government laboratory of limited size. But through the dedication and abilities of its staff of scientists, including such leading investigators as Joseph Goldberger, the Laboratory became an effective force, solving such medical riddles as the cause of pellagra and providing the knowledge for prevention of that and other problems, such as Rocky Mountain spotted fever.

Through most of this period the Laboratory concentrated its efforts on infectious diseases (or what were thought to be infectious), but in 1930 the Congress broadened the scope of responsibility of the institution to the virtually unlimited mission of "....ascertaining the cause,

prevention and cure of disease." It was then that the name "The National Institute of Health" was given to the Laboratory.

The modern era of NIH, as well as of biomedical research in the United States, began when the Government and non-Government research laboratories, mostly in academic institutions, joined their efforts in carrying out research in World War II. To meet the urgent health problems of the armed services, the Government turned to the established non-Federal academic and independent laboratories for help in conducting vital research. Grants and contracts were awarded for the support of essential investigations. The arrangement worked well. The newly formed partnerships accelerated progress in research and development across the spectrum.

By the war's end, the U.S. Office of Scientific Research and Development was administering a large number of medically related research projects--some 250 were being conducted at universities, medical schools, hospitals, and pharmaceutical companies. The OSRD decided to turn over the Government's administration of these projects to the National Institute of Health. This decision not only confirmed the agency's role as the principal biomedical research arm of the Federal Government, it also established Government support of research in non-Government institutions as the dominant mechanism for carrying out such investigations.

Increases in the NIH budget have been spectacular since the addition of the extramural dimension to its programs. The total budget of the NIH grew at an astounding average rate of 24 percent per year for more than 20 years from 1945 to 1968.

The rapid expansion of the NIH organization has mirrored public concern about specific diseases and general categories of health problems. The names of the twelve institutes constitute a kind of historical catalog, as for example, the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute on Aging. From the beginning, however, even though many of the institutes were given disease-specific missions, our commitment to basic research has been

sustained and is a substantial component in the research programs of each of the institutes. In the early 1970s, the fraction of the total NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

During recent years between 10.5 and 12 percent of our total budget has been spent for intramural research and training in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural programs.

Since the early 1950s, large numbers of young scientists have come to the NIH for periods of several years and then moved on to a university or academic medical center. In fact, this may be one of the great contributions of the NIH: it has greatly changed the university structure in this country. The building of many great research-oriented universities rests heavily on NIH support, and currently more than 63 percent of all the health-related research in universities is supported by NIH. Furthermore, the linkages that develop at NIH are often enduring. Scientists who move to universities often continue to collaborate with the person under whom they trained, they return for seminars, they invite NIH scientists to visit them in their new setting, so that there is a great deal of continual interaction and collaboration.

As large as the intramural program is, however, almost 90 percent of the NIH's budget is devoted to extramural awards for research and research training and the administrative costs entailed.

By far the largest part of NIH research takes place in some 1650 universities, medical schools, research hospitals, independent and industrial laboratories in the United States and in many other countries. Last year the NIH funded more than 28,000 research and research training projects involving more than 50,000 non-Federal scientists. Of all the states, Massachusetts has the highest per-capita share of NIH funding--a total of more than $473 million in 1986.

The key mechanism used by NIH for support of biomedical research is the investigator-initiated project grant made in response to proposals submitted on the initiative of researchers who outline the questions they wish to study, specify their research strategies, and estimate their costs. Such grants are used for supporting the majority of our extramural research, and well over half of our total budget is allocated to these projects. Such investigator-initiated research draws upon the expertise and intuition of practically the entire American scientific community. In recent years the number and quality of research proposals has increased steadily, and have outstripped our ability to fund them--2 percent average growth since 1968, but 5-6 percent since 1982.

We now find ourselves having to turn down more and more applications that a few years ago would certainly have been funded. At this time we are able to make awards for the support of research proposed in only about a third of fully eligible applications.

In the absence of funding from Federal sources, it too often is necessary for an investigator to defer or even abandon promising research projects. Perhaps more significant in the long run is the effect on the young researcher who, after seven to ten years of post-college training, has about a one-in-three chance of gaining independent funding from NIH. We cannot quantify with precision how many decide to consider a change in their career path in the face of such odds, but there are indications that our concerns about this problem are justified. For example, a recent analysis shows that, on the average, NIH-supported investigators are older today than in previous years. The average age of applicants in 1979 was 41.9 years, and in 1985 it was a full year older--42.9 years.

There has been a persistent decline in the number of younger applicants for traditional NIH grants. The percentage of all applicants who were under 36 went down from 26.1 percent in 1979 to 13.4 percent in 1986. Stated in number of applications, investigators who were under 36 filed 3,466 R01 project grant applications in 1979 and a substantially smaller number, 2,052, in 1986. That was a drop of 41 percent. The decline was even sharper among applicants under 31 where the drop was 79

percent. The significance of these changes is underlined by the fact that investigators 30 and under continue to receive the best priority scores. The second best group is in the band of ages from 31 to 35.

For those of us who are intimately involved in biomedical research, trends such as those I have mentioned have special meaning that may not be readily apparent to the general public. For that reason I wish to express special appreciation to the Massachusetts Centennial Committee for its effective use of the centennial observance as an occasion to translate the current and future needs and benefits of biomedical research.

In your position papers you have concisely presented such urgent matters as science education in the secondary schools, resources for postgraduate research training, and the problems of obsolescence and deterioration of buildings and equipment.

Thus the Massachusetts observance of the NIH centennial, while paying eloquent tribute to the progress of the past hundred years, does not suggest that we can rest on such accomplishments, but responsibly addresses the issues, the problems, and the great opportunities of the years ahead.

There need be no better reason for conducting biomedical research than the improvement of human health. This is central to American policy regarding G overnment support of such activities. Always present is the attraction felt by scientists for research as a means for meeting the insatiable human desire to know. In recent years, a third justification for Government support of research has come into prominence--biomedical research as a foundation for biotechnology. The Administration and the Congress have become interested in the economic consequences of our national investment in biomedical research that has been responsible for the emergence of biotechnology. Thus the subject has become an element of Federal policy that is in the process of being refined.

A descriptive statement of the role of science in the life of people throughout the world appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads,

"....To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability are of preeminent concern, and national policy concerning biomedical research is of surpassing importance in all countries. Its significance is truly universal. The great British statesman Disraeli said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."[3]

In closing, may I once again express for NIH our deepest appreciation for the recognition being given to our centennial and our gratitude for your continued friendship.

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REMARKS*

by

James B. Wyngaarden, M.D.**

Sir James, our debt of gratitude to you and to your associates of the Medical Research Council is great indeed. Your thoughtfulness in organizing this conference to celebrate the centennial anniversary of the National Institutes of Health is but one of the many acts of friendship that have made our trans-Atlantic collaboration so effective and personally satisfying to your American colleagues.

The theme you have chosen for this conference is singularly appropriate. It is suggestive of the future, the essential element of any meaningful anniversary observance. As an examination of "Prospects for Improvement in Health Care from Medical Research," it is premised upon an appreciation of the value of research and its indispensable role in developing new measures for health care. It brings to mind a one-sentence description of the purpose of the NIH that first was published about a decade ago. The mission of the NIH according to the statement is "....to uncover new knowledge that will lead to better health for everyone."

In his essay on the "Organization and the Growth of Scientific Knowledge," Sir Harold Himsworth, the former Secretary and later Deputy Chairman of the MRC, commented, "When future historians look back at the period in which we are now living they are likely to see it as that time in which scientific knowledge emerged from its adolescence to become a major factor in the affairs of human societies." Sir Harold also noted that, "Any expert activity that becomes socially important is, ipso facto, driven to come to terms with the society in which it operates."[2] He characterized organizations such as the MRC and the NIH as instruments whose purposes are to meet both the needs of science and the human expectations that the

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*Opening Statement at the Medical Research Council Symposium in honor of the NIH Centennial at the Royal Institution of Great Britain in London, England, October 2, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

achievements of science have aroused. "Such organizations," he said, "are normally in contact with the extremes of scientific activity, that which is mission oriented and has direct social relevance and that which is quite fundamental."[3]

The early history of the NIH was closely entwined with European science of the late nineteenth century. The opening of a one-room laboratory by Dr. Joseph J. Kinyoun in 1887, in the attic of the Marine Hospital Service facility on Staten Island in the port of New York, had a highly specific purpose. It was to help the United States ward off the importation of cholera and yellow fever, and its principal function was to provide diagnostic intelligence in the war against pestilence.

While in his early twenties, Kinyoun was sent to Europe for postdoctoral study with the pioneers in microbiology, in the hope that new insights from the laboratories of Koch, and Pasteur and Lister might suggest measures for preventing a wave of cholera in the United States. Upon his return he set up the laboratory on Staten Island that in time became the National Institute of Health.

The mission at the Laboratory was clearly defined, but the young doctor's goal was to establish an activity that might in time serve a more general and long-term purpose. Soon after he opened the Laboratory Dr. Kinyoun arranged to have himself assigned temporarily to Europe once again so that he might study in the laboratories there. He was careful to acquaint Congress and the American people of the importance of what was taking place in Europe and its relevance to his goals for the new Laboratory. He told the Congress that the new Laboratory should form the nucleus of a national facility, and that it should be developed along the lines of those established in Germany, France, and England.

The first steps toward realization of Dr. Kinyoun's goal to make the Laboratory a national resource were taken when it was moved to Washington and eventually to a downtown location there where it remained for more than 40 years. In 1930 the relatively small Laboratory was named the National Institute of Health, and with it the challenging assignment of "....ascertaining the cause, prevention and cure of disease." But the modern

era of NIH, as well as of biomedical research in the United States began in the early 1940s when the Government and non-Governmental laboratories joined their efforts in carrying out research during World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the armed services, the Government turned to the established academic and non-Federal independent laboratories for help in conducting vital research. The partnerships were successful in accelerating progress in research and development across the spectrum.

Some 250 medically related projects were in progress at wars end in universities, medical schools, hospitals, and pharmaceutical companies. It was decided that the projects should be continued and with the disbanding of the wartime Office of Scientific Research and Development they were turned over to the National Institute of Health. This was a critical event in the history of the NIH for it confirmed our role as the principal biomedical research arm of the Federal Government. It also established Government support of research in non-Government institutions as the dominant mechanism for carrying out biomedical research.

The Government's decision to continue the research programs through the use of grants had been urged by Vannevar Bush, scientist-educator who was a principal advisor to President Roosevelt. When the end of the war was foreseen, the President asked Bush to chart a course for postwar science. In his response, that proved to be an American landmark in science policy, Dr. Bush strongly recommended that the Government continue to invest in scientific research, particularly in the realm of health. He pointed out the crucial importance of academic institutions in carrying out such Government activity.

Bush characterized public and private colleges, universities and research institutions as "wellsprings of knowledge and understanding." He said that "As long as they are vigorous and healthy and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge." Scientific progress, he said, "....results from the free play of free intellects working on subjects of their own choice in the manner dictated by their curiosity for explanation of the unknown."[4]

We have seen the fruits of that prescription for scientific progress. The surge of discovery that has taken place in the biosciences in a little over a generation is without precedent, and it is still gathering strength.

In a little over 40 years, the number of projects funded by the NIH has increased well over one hundredfold. Our extramural program began with the 250 projects transferred to the NIH in 1945, and last year, when all types of projects were counted, NIH funded more than 28,000 projects involving approximately 50,000 scientists in more than 1,600 institutions in the United States.

Since 1945 the growth of the NIH has been essentially continuous through the administrations of eight Presidents and twenty Congresses. The support we have received from our champions in Congress and in the Executive Branch, regardless of their party affiliation, encourages us to look to the future with optimism, for it is clear that along with the great public concern about good health there is understanding of the need for new knowledge if we are to improve health care. It is clear that we are expected to serve the public interest. Our agency is called the National Institutes of Health, not the National Institutes of Biomedical Research.

Almost two years ago when I was preparing to testify before the congressional appropriations committee in support of our 1987 budget request, I came across a staff study by the Heritage Foundation, an organization not noted for encouraging Federal expenditures, in fact quite the opposite. The title of the study was "Slashing the Deficit," and it advocated in detail how the programs of practically every Federal agency might be cut.

In the discussion of the NIH budget, after a bit of obligatory grumbling, the staff commented, "Basic biomedical research is one of the few activities funded through Washington which is apparently a Federal responsibility." The report went on, "Historically, the benefits of such research have outstripped the taxpayers cost."[5] You may be sure I called the attention of the congressional committees to the Foundation's report.

I am encouraged to believe that as we complete our first century the NIH has met the challenge articulated by Sir Harold, and that we have come to terms with the society in which we operate, and that we fully encompass the spectrum of scientific activity from the one extreme of "direct social relevance," and to the other, the realm of basic research. One of the important uses of our centennial observances has been to provide a platform for reminding the people of our country, and elsewhere, that organizations such as the NIH, the MRC, and our counterparts in other countries such as France, Italy, and Sweden are able to meet the requirements of social relevance because we have the resources to maintain the fundamental search.

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[4]Bush, Vannevar, "Science--The Endless Frontier," U.S. Government Printing Office, Washington, D.C., 1945, p. 12.

[5]"Slashing the Deficit--Fiscal 1987," a proposal by the staff of the Heritage Foundation, Heritage Foundation, Washington, D.C., 1986, p. 90.

REMARKS*

by

James B. Wyngaarden, M.D.**

Once again I will take the occasion to express on behalf of the National Institutes of Health our gratitude to the MRC for planning and conducting the magnificent conference that has just been held to celebrate the centennial of the National Institutes of Health. I also wish to say to our friends from the other European countries, with whom we have collaborated over the years, how much we are indebted to them for participating in what to us has been a memorable time.

It has occurred to me that two of my favorite quotations, taken together, constitute an abstract summation of the theme of this conference.

The first is from the words of Disraeli, who spoke of the political significance of our endeavors when he said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."

My second quotation appears on the wall of the Great Hall of the National Academy of Sciences in Washington. It expresses the scientist's view and could well be a toast for an occasion such as this. It is addressed, "To Science; Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law, and Eternal Guide to Truth."

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*Presented at the Medical Research Council dinner in honor of the NIH Centennial, London, England, October 2, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

REMARKS*

by

James B. Wyngaarden, M.D.**

- From "Politics, Science and Dread Disease" by Stephen P. Strickland: (Regarding efforts in 1971 in support of the Conquest of Cancer bill then in the Senate), "Mary Lasker....suggested to her friend Ann Landers....that she help spread the word about the importance of the Conquest of Cancer bill. Ms. Landers did so in April, urging her readers to become part of the mightiest offensive against a single disease in the history of our country. To join that mighty effort one had only to write his Senator. The response was overwhelming. Senator John Tunney, for example, estimated that he got approximately 25,000 pieces of mail as a result of the Landers column."

  Another author, Natalie Spingarn, telling the story of the Cancer bill wrote in her book, "Heartbeat," that "an urgent 'Write your Senator' appeal from syndicated columnist Ann Landers produced hundreds of thousands of supporting letters."

  The fantastic response from the appeal by Ann Landers is firmly established in the folklore of the Senate, and of the NIH as well. It was not reported in any official history, but some recall that NIH and NCI offices were drafted to assist senatorial offices in writing responses to the flood of Landers-generated mail.

- For several years, Ann Landers has been the most widely read source of information on the critical importance of using animals as models in biomedical research. Because of the high regard in which she is held by her tens of millions of readers, her reasoned and temperate defense of research with animals has accomplished for science something that is far beyond the reach of the NIH and FASEB. Just as her columns on

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*Presented at the FASEB luncheon honoring Ann Landers, Bethesda, Maryland, October 7, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

the Conquest of Cancer generated large amounts of mail, I would guess that her columns on animals caused an outpouring, but with a substantial amount of it aimed at her. From the experience we have had with communications from the activists groups, I must admire her courage for voluntarily and repeatedly subjecting herself to the barrage in order to state her conviction about the need for animal models. All of the biological sciences are indebted to Ann Landers.

- Ann has helped NIH in many ways, but I think I should call attention to an occasion when one of our officials helped her. Two years ago I served as her helper, or perhaps more specifically her chef's assistant, when we prepared a notorious fish stew at the March of Dimes Celebrity Gala, here in Washington.

THE NATIONAL INSTITUTES OF HEALTH AT THE CENTURY MARK*

by

James B. Wyngaarden**

Thank you, Mr. Hutchinson, for that kind introduction.

I would like to express my appreciation to the Commonwealth Club for the honor of speaking to you today. The list of previous speakers reads like Who's Who in The World, and I am privileged to be placed in the company of former speakers, such as Secretary of Defense Casper Weinberger.

My address is entitled, "The National Institutes of Health at the Century Mark." Today I would like to tell you something about this remarkable institution that is celebrating its 100th anniversary this year. In a taped interview for use in an NIH Centennial presentation, scientist and author Lewis Thomas said the following, "I think the general public is aware of the fact that we are in the early stages of a genuine revolution in biological science. The effects that this revolution is now having and will have in the years ahead on medicine are simply incalculable. All this had its beginnings at NIH, starting around 40 years ago. All by itself this magnificent institution stands as the most brilliant social invention of the 20th century anywhere." That is very high praise indeed, and it reflects the fact that medical research conducted by the National Institutes of Health has improved the health and well-being of almost every man, woman, and child in the United States and, indeed, throughout much of the world. The American people deserve to know more about this institution, which is one of the treasures of this country, and that is what I hope to accomplish in this address. Let me first describe briefly the National Institutes of Health as it is today, then review some of its early history and some of its accomplishments, and finally mention some of the enormous challenges that still lie ahead.

The National Institutes of Health is the principal agency of the Federal government devoted to conducting and funding biomedical research. Its legislative charge is really quite simple, to uncover new knowledge of potential benefit to the health of the people. The headquarters of the NIH is in Bethesda, Maryland, where we have a campus of about 320 acres with 40 buildings. In appearance and in working style, it resembles a university far more than a traditional government agency. The largest building is a 500-bed clinical research center that includes about 500 laboratories for research related to a wide range of diseases. Altogether we have about 13,000 employees, including about 3,500 doctoral level scientists. Of the latter number, about 1500 are members of our permanent staff and about 2000 are younger medical and basic scientists working in association with more senior people. We conduct a substantial amount of research on the Bethesda campus,

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*Address at The Commonwealth Club of California, San Francisco, California, October 9, 1987.

**Director, National Institutes of Health, Bethesda, MD.

and many important discoveries have been made in our intramural laboratories. Many of our scientists have worldwide reputations, and four have received Nobel Prizes.

But by far the greatest amount of medical research funded by the National Institutes of Health is conducted not in Bethesda, but by scientists in universities, medical schools, and other research institutions throughout the country. Almost 90 percent of our budget is expended in a system of research grants and contracts that support the creative ideas of individual scientists or teams of research workers, in laboratories or hospitals or specialized research centers, distributed throughout our 50 states. This year we are supporting some 28,000 research and research training projects involving over 50,000 scientists in about 1650 institutions in the United States, plus some in other countries. The projects that we support are selected in open competition, and in the evaluation of research applications we rely very heavily on the appraisals of non-Federal scientists who serve as reviewers for the National Institutes of Health. In this manner we utilize the expertise of scientists throughout the land, both in the conduct of research and in the evaluation of research proposals.

The extramural research support program provides salaries for research workers and funds for supplies, equipment, and necessary travel. In previous years we have built research facilties. In addition, we support the training and development of graduate students and young scientists who will be the leaders of tomorrow. The support by NIH has transformed the American universities and medical schools into the most outstanding biomedical research institutions of the world. American scientists now win the majority of Nobel Prizes for Physiology or Medicine. Sixty-five Americans and perhaps another seven foreign Nobel Laureates have received support from NIH before winning the Prize.

I am happy to tell you that scientists from the state of California compete very well for financial support from the National Institutes of Health. In fact California receives more NIH funds than any other state. During 1986, for example, $649.5 million were awarded to California institutions.

The National Institutes of Health is a complex institution. It is comprised of 12 rather autonomous Institutes and 6 major operating divisions. Most of the Institutes are organized around groups of related disorders. Some of these Institutes are familiar to you because they are frequently in the news. For example, most of you will have heard of the National Cancer Institute, the National Heart, Lung and Blood Institute, and the National Institute on Dental Research. Other prominent Institutes are the National Institute of Child Health and Human Development, the National Institute on Aging, the National Eye Institute, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Allergy and Infectious Diseases. Last year the Congress divided one of our larger, multi-purpose Institutes into two, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Finally we have two very broad Institutes that are not so much organized around specific disease areas as around fields. One of these is the National Institute of Environmental Health Sciences, and it is the only Institute whose headquarters are not in Bethesda, in this case they are in the Research Triangle Park of North Carolina. The other, the National Institute

of General Medical Sciences, supports very basic studies on the nature of living systems, studies that are not clearly linked to a specific disease area. For example, NIGMS supported a great deal of the fundamental work in genetics and in molecular biology that has led to the biotechnology revolution and the new biotechnology industry. Some of you will have noticed that I have not mentioned the National Institute of Mental Health. This Institute was originally part of the National Institutes of Health, but about 20 years ago it was split off into a separate agency when its mission was greatly expanded to include many community services such as mental health clinics. Later it was combined with two other Institutes that deal with drug addiction and alcoholism, and these three areas comprise a sister agency entitled the Alcohol, Drug Abuse, and Mental Health Administration.

I will mention only two of our several divisions. One of these is the National Library of Medicine, one of the largest medical libraries of the world, and one that has pioneered in computerized telephonic communications. Almost every hospital in this country, for example, has a linkage with the National Library of Medicine and can very quickly receive references and abstracts of almost every important medical work. Thus the world's medical literature can make an immediate difference in patient care. Finally, last year the Congress created a new division, entitled the National Center for Nursing Research, which is now in a phase of rapid growth.

Each one of these entities conducts research in our intramural laboratories and also funds research in institutions throughout the country. Each has programs that extend from very basic research to highly targeted work, work for example on specific diseases, or in evaluation of new diagnostic or therapeutic approaches. Between the work conducted in our own laboratories and that supported elsewhere, each Institute has a broad and extensive program for advancing health through discovery of new knowledge.

Each year the President's budget includes a proposal for funding of the NIH, as it does for all Federal agencies. Each year the Appropriations Subcommittees in the House of Representatives and in the Senate hold hearings on our budget in which we discuss our proposals and plans for the next year. Many other groups are also invited to testify. These groups include organizations representing the medical colleges, the universities, independent research institutions, voluntary health agencies, such as the American Cancer Society or the American Heart Association, and even individuals who want to call the attention of the Congress to the need for additional research in particular disorders of concern to them. Such testimony has built our research programs in cancer, heart disease, cystic fibrosis, Alzheimer's disease, AIDS, and many other areas. There is no other country in the world that goes about developing its health research budget the way we do; it is a marvelously open and democratic system, and the programs of the NIH reflect the priorities of the public as well as of the scientists.

The total budget of the National Institutes of Health in 1987 was over $6 billion. That represents a 70 percent increase in just the past 5 years, and this increase reflects the sense of the Congress that increased support for biomedical research will result in more rapid progress in solving many of our pressing health problems. It is certain that we have never had the kind of insights into normal life processes and the mechanisms of disease that we presently have. I believe we are poised for truly important advances in the next decade.

I would like now to discuss a little bit of history and in rather broad brush strokes to paint the development of the National Institutes of Health in its first 100 years. We trace our origin to a one-room attic laboratory in the Marine Hospital on Staten Island in New York harbor. The laboratory was established to do research on infectious diseases that were appearing in near epidemic proportions, particularly during the summer months. Many of these worrisome diseases were thought to be entering the country with European immigrants. The relationship of specific bacteria to specific diseases was just being discovered in the laboratories of Europe, particularly those of Pasteur in Paris and Koch in Berlin. Methods for culturing and identifying the organisms that cause tuberculosis, cholera, and plague were beginning to influence medical practice in Europe, and the laboratory on Staten Island was set up to recognize and control these diseases in the port of New York. The first Director was a 26-year old physician, named Joseph Kinyoun, who had training in bacteriology, and had visited both Koch and Pasteur. The chief investment in the laboratory was $300 for a new Zeiss microscope. Just two months after the Laboratory of Hygiene, as it was called, went into operation Kinyoun established the diagnosis of cholera in an immigrant boy who had died two days after arrival at the port of New York. By quarantining the other 400 steerage passengers on the ship, Kinyoun averted an important potential source contributing to the cholera epidemic of 1887.

Recently I also learned an anecdote about Dr. Kinyoun and San Francisco which has left me to hope that I receive better treatment here than did the first NIH Director. In 1889 Dr. Kinyoun was sent out to San Francisco to try to prevent the entry of bubonic plague into the country as a result of an epidemic in China. Using his microscope Kinyoun confirmed a case of plague in Chinatown, but the City Fathers would hear nothing of it, escalated their greivance to the state level, and had Dr. Kinyoun shipped back East. For years the Governor continued to deny the existence of plague in California and denounced Kinyoun until other experts, from Johns Hopkins University in Baltimore in particular, confirmed the epidemic and the Surgeon General finally adopted recommendations that essentially eliminated the plague in 1905.

By this time the Laboratory of Hygiene had been moved from New York to Washington, D.C., which underscored its growing role as a national resource. Its scientists contributed to the solution of the number of important health problems, among them Rocky Mountain Spotted Fever, tularemia, psittacosis, and pellagra. Many of these diseases are scarcely recognizable to the general public today because they have been effectively controlled or eliminated by past research. The Ransdall Act of 1930 was a landmark in NIH history. It changed the name of the Hygienic Laboratory to the National Institute of Health, and expanded its concentration on infectious diseases to the broader mission of "ascertaining the cause, prevention, and cure of disease." In 1938 the NIH moved to its present location in Bethesda, Maryland, and in 1947 its name was changed to the National Institutes of Health. Over the next several years the Congress greatly enlarged its scope with the creation of a number of new Institutes.

The character of the NIH had changed dramatically during and just after World War II. During its first 50 years, the NIH and its predecessor, the Hygienic Laboratory, was an essentially independent, free-standing laboratory of limited size concentrating on infectious disease problems. During the second

World War the Office of Scientific Research and Development turned to established non-Federal laboratories to conduct research in support of the war effort. This partnership greatly accelerated biomedical research and development across the spectrum from the most basic studies to the wide-spread application of new means for prevention, diagnosis, and treatment of disease. The postwar transfer of 250 such projects at universities and medical schools to the National Institute of Health marked the beginning of its program of extramural research support. Many of these projects transferred to the NIH involved research on penicillin and, when the price of the drug fell drastically in late 1945, NIH used the extra money to expand its grant program. Not everyone was comfortable with this expansion at the time. There were skeptics who feared that government funding of research would lead to government control of research in support of targeted objectives, and inhibition of scientific freedom. But leaders in the Administration and the Congress and in the academic world who understood the processes of science devised policies and practices that protected free inquiry and the exploration of original ideas. The great strength of the current biomedical scientific enterprise owes much to the wise leaders at the National Institutes of Health in the 1940s and 1950s. Today NIH remains committed to the basic tenet of the philosophy upon which the scientific method rests, namely the integrity and independence of the research worker and his or her freedom from control, direction, regimentation, and outside interference.

Time will permit citing only a few of the accomplishments of NIH that have helped to improve the health of the American people. One major theme is that of infection in which NIH-supported work has contributed to recognition of new infectious agents and disorders, such as diseases caused by slow viruses, appropriate use of antibiotics, an understanding of the role and complexity of the immune system, and the development of a number of effective vaccines against polio, measles, mumps, hepatitis, and pertussis. In the cardio-vascular field advances include new surgical procedures for congenital heart disease, a medical procedure for the closure of patent ductus arteriosis developed here in San Francisco, advances in the understanding of mechanisms and control of hypertension, recognition of risk factors such as cholesterol, overweight, and smoking. NIH supported studies and treatment methods have contributed significantly to a 35 percent reduction in cardiovascular deaths and a 40 percent reduction in cerebral vascular deaths in the past 20 years. As a result of studies conducted and supported by the National Cancer Institute, 50 percent of childhood cancers are now permanently curable, 70 percent of Hodgkin's Disease is now curable, treatment for breast cancer, testicular cancer, ovarian cancer, and many others are much improved, and new insights have been gained into cancer causation and prevention. Dental cavities of children and teenagers are much reduced in frequency, owing to fluoridation procedures developed in the National Institute of Dental Research.

Over 60 percent of all of the research supported by NIH is basic research, conducted in order to increase our understanding of living systems, and without a specific application in mind at the time. I want to stress how important I think it is that we continue to devote adequate resources to basic research and that this is a role that only government can fill. It is an investment in knowledge, but it is also a long-term investment in health. The investment in genetics of bacteria and viruses in the 1950s led directly to an

expanded knowledge of human genetics and of the role of genetic factors in many diseases. It also led to the discovery of the techniques of recombinant DNA research, and to the establishment of the new biotechnology industry in which the United States is the world leader and which is so prominent here in California. This research also led to the recognition of oncogenes, cellular genetic elements that play important roles in cancer predisposition, very important work on oncogenes done by Drs. Bishop and Varmus at UCSF.

The earlier investments in basic research account for much of the rapid progress that has been made in the battle with AIDS -- discoveries of T-cell growth factor or interleukin 2, other retroviruses in man, recombinant DNA techniques, and in immunology during the previous 10 years are directly responsible for the rapid identification of the AIDS virus, and for the introduction of antibody testing procedures that have advanced the understanding of the natural history and transmission of disease and have assured a virtually safe blood supply for transfusions and hemophiliac children. None of this would have been possible had the AIDS epidemic burst upon us 10 years earlier.

In closing let me say a few words about the second century of NIH. There is a symmetry between the infectious disease epidemics that launched the NIH in 1887 and the current scourge of AIDS that preoccupies us in 1987. We are vigorously engaged in identifying new drugs that will be effective in AIDS, and also in attempts to develop vaccines that will protect against AIDS. I want to stress that animal experimentation, particularly with chimpanzees, is absolutely essential to progress against AIDS, especially in the development a vaccine. We also continue to do battle with the other major killers, cancer and heart disease, as well as with the chronic diseases that limit the quality of life, such as arthritis, Alzheimer's disease, and other neurological disorders in science. There are occasional breakthroughs of extraordinary excitement that suddenly open new vistas. One such may be the recognition of the magainins in frog skin, short poly-peptides that appear to have amazing potential as new antibiotic agents. Another may be the new insights that we anticipate will emerge from sequencing the human genome. In most areas, however, it is the incremental accretion of knowledge that brings about gradual improvement, and periodically raises a field to a new plateau from which one can view new solutions. Health is a universal aspiration. The United States is pre-eminent in health research. The linkages forged with foreign scientists, who come here to learn, generate powerful forces for understanding among peoples. The great British statesman Disraeli remarked that the health of the people is the foundation on which all happiness and all their powers as a state depend. In closing, I would like to cite a short passage from a report of the Heritage Foundation, which is not noted for advocating Federal expenditures:

> "Basic biomedical research is one of the few activities funded through Washington which is appropriately a federal responsibility. . . . Historically, the benefits of such research have outstripped the taxpayers cost." (1)

Lewis Thomas said of NIH that it "is a standing proof that, at least once in a while, the government possesses the capacity to do something unique, imaginative, useful and altogether right." (2)

I could not have said it better.

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1. "Slashing the Deficit," a proposal by the Staff of the Heritage Foundation. The Heritage Foundation, Washington, D.C., 1986, p. 90.

2. "NIH: An Account of Research in Its Laboratories and Clinics," the forward, DeWitt Stetten, Jr., and W. T. Carrigan (Eds.), Academic Press, Inc., 1984, Orlando, Florida.

LOOKING FORWARD TO THE NEXT CENTURY*

BY

JAMES B. WYNGAARDEN, **

IT IS MY HONOR AND EXTREME PLEASURE TO WELCOME YOU TO THIS CEREMONY THAT MARKS ANOTHER HIGH POINT IN THE OBSERVANCE OF THE NIH CENTENNIAL THAT BEGAN EXACTLY A YEAR AGO. AT THE TIME OF THE OFFICIAL OPENING WE TALKED OF A NUMBER OF EVENTS THAT WERE PLANNED TO HONOR THE INSTITUTION, ITS PEOPLE, AND ITS ACCOMPLISHMENTS, BUT I THINK NONE OF US HAD A FULL APPRECIATION OF WHAT THE YEAR WOULD BRING IN THE WAY OF THE OUTPOURING OF GOODWILL.

THE NATIONAL INSTITUTES OF HEALTH HAS BEEN, OR SHORTLY WILL BE, THE HONOREE AT BIRTHDAY CELEBRATIONS IN MANY DIFFERENT CITIES IN THE UNITED STATES, AND IN JAPAN, AUSTRALIA, NEW ZEALAND, GERMANY, YUGOSLAVIA, FRANCE, THE UNITED KINGDOM, CANADA, AND MEXICO. EACH EVENT HAD ITS OWN SPECIAL FLAVOR, BUT ALL WERE EXCITING AND GRATIFYING EXPRESSIONS OF UNDERSTANDING FOR AND APPRECIATION OF THE IMPORTANCE OF BIOMEDICAL RESEARCH.

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*WELCOMING REMARKS PRESENTED AT THE COMMEMORATIVE CEREMONY MARKING THE CLOSING OF THE NIH CENTENNIAL OBSERVANCE, BETHESDA, MARYLAND, OCTOBER 16, 1987.

**DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

BECAUSE OF THE CENTENNIAL OBSERVANCE THE NIH HAS BEEN THE SUBJECT OF A LARGE NUMBER OF FEATURE ARTICLES IN MAGAZINES AND NEWSPAPERS, INCLUDING THE PRINCIPAL NATIONAL PUBLICATIONS. RADIO AND TELEVISION STATIONS NATIONWIDE HAVE TOLD THEIR AUDIENCES OF THE IMPORTANCE OF BIOMEDICAL RESEARCH AND ITS ROLE IN IMPROVEMENT OF HEALTH.

WE HAVE BEEN HIGHLY PLEASED WITH THE SERIES OF FOUR ONE-HOUR TELEVISION PROGRAMS TITLED "THE HEALTH CENTURY." THE FOUR PROGRAMS CONVEYED THE MEANING AND EXCITEMENT OF BIOMEDICAL RESEARCH TO A NATIONWIDE AUDIENCE THROUGH THE PUBLIC BROADCASTING SERVICE. ALTHOUGH THE FIRST AIRING OF THE SERIES WAS COMPLETED LAST MONDAY, I AM SURE IT WILL BE RERUN A NUMBER OF TIMES ON INDIVIDUAL PBS STATIONS, AND WILL BE AN IMPORTANT CLASSROOM RESOURCE. I MUST ALSO MENTION THE BOOK "_____" BY Edward Shorter, THAT CONSTITUTES A LAST LEGACY.

THE FILM, THE BOOK, OUR CONGRESSIONAL BREAKFASTS AND OTHER IMPORTANT CENTENNIAL ACTIVITIES WERE POSSIBLE ONLY BECAUSE OF THE GENEROUS AND PUBLIC SPIRITED GIFTS FROM A SPECIAL GROUP OF OUR PARTNERS IN THIS CENTENNIAL OBSERVANCE. THEIR NAMES ARE LISTED IN THE PROGRAM, AND I THINK THAT AT THIS TIME, A SHOW OF OUR APPRECIATION WOULD BE APPROPRIATE.

A CENTRAL THEME OF OUR MANY MESSAGES DURING THE YEAR HAS BEEN TO STRESS THE IMPORTANCE AND THE EFFECTIVENESS OF THE

PARTNERSHIP OF ACADEMIA, INDUSTRY AND THE FEDERAL GOVERNMENT IN THE SUPPORT AND CONDUCT OF BIOMEDICAL RESEARCH. WE HAVE SOUGHT TO MAKE THE AMERICAN PEOPLE BETTER AWARE OF THE IMPORTANCE OF BIOMEDICAL RESEARCH, THE NEED FOR ITS CONTINUED SUPPORT, AND THE ABSOLUTE IMPORTANCE OF CONTINUOUS REPLENISHMENT OF ITS COMMUNITY OF ABLE, WELL-TRAINED AND DEVOTED SCIENTISTS.

SUCH HAVE BEEN THE GOALS OF THE NIH CENTENNIAL ACTIVITIES. WE FEEL THAT WE HAVE GONE A LONG WAY TOWARD MEETING THEM, AND THAT THIS CEREMONY TODAY IS IN PART AN ACKNOWLEDGEMENT OF THAT SUCCESS.

RECEPTION BEFORE COMMEMORATIVE CEREMONY

Friday, October 16, at 11:45 am
1/Wilson Hall

Mr. Flavin will introduce Dr. Wyngaarden. Then,

DR. WYNGAARDEN:

It is a pleasure to meet with you this morning to acknowledge the work of those who have been responsible for the success of our Centennial observance. It has been a very busy year, and the observances have taken many forms. Some of the people here have been planning ceremonies and other functions for a year and a half! And so it is time for us to stop and say thank you to these groups.

First let us honor the Underwriters Committee and the Underwriters Steering Committee -- executives from 15 companies whose generous contributions made possible many of this year's activities.

Next is the NIH Centennial Committee, whose members represented outside organizations and brought many points of view to our celebration. Their counsel under the leadership of Don Fredrickson has been invaluable to us.

The chairmen of the subcommittee responsible for planning each activitiy made up the NIH Centennial Events Committee. Many of these people have been involved in Centennial planning on a daily basis for months.

Former NIH researchers in many parts of this country and in other countries have planned special observances of the NIH Centennial, and to them we say thank you.

We would also like to acknowledge the support of our international colleagues, many of whom have spent time in our laboratories, with whom we have had such good working relationships over the years.

The Centennial activities have been many and varied: the Opening Ceremony a year ago; the Congressional Breakfasts, where Nobel Laureates and other eminent scientists briefed Members of Congress and their staffs on the latest developments in biomedical research; the public TV series on the Health Century and the companion book; Employee Recognition Day, when all our employees had their day in the sun (pause) and heat; the 2-day Open House for our employees and the public, and for 3200 junior and senior high school students; the Alumni Reunion and Symposium weekend, and this Closing Ceremony. We have met old friends and made new ones, and we have reaffirmed our commitment to our common purpose.

One of the most exciting aspects of our year was bringing to Washington outstanding high school science students and their teachers from 55 states and territories and the District of Columbia. In their three days here, they visited several laboratories at NIH, impressing everyone they met with

their eagerness and ability, and giving us real hope for the second hundred years. These students and teachers breakfasted on Capitol Hill and met with many of their Representatives and Senators, lunched with Nobel Laureates and NIH research scientists, and dined at the National Academy of Sciences as guests of the Howard Hughes Medical Institute.

Three of these young people have come back today to present NIH Centennial medals to some of our guests. First is Jerome Battle of McKinley High School in the District of Columbia, who will present a medal to Secretary Bowen.

Mr. Battle: Mr. Secretary, we appreciate having had the opportunity the Department afforded us to visit the NIH during this Centennial year. We promise to make the future as exciting as the past century has been.

Dr. Bowen: Thank you, Mr. Battle. I appreciate your kind words and fully expect that you and the other students will keep that promise.

DR. WYNGAARDEN:

Thank you, Mr. Secretary. Laura Coltrane of Denbigh High School in Newport News, Virginia, will present a medal to Dr. Robert E. Windom, Assistant Secretary for Health.

Ms. Coltrane: Dr. Windom, my fellow students and I thank you for the activities of the Public Health Service in support of biomedical research and for your inspiring words at our luncheon last February.

Dr. Windom presents his remarks.

DR. WYNGAARDEN:

Thank you, Dr. Windom. And now Catherine Johnson of Snow Hill High School in Snow Hill, Maryland, will present a medal to Dr. C. Everett Koop, Surgeon General of the Public Health Service. Dr. Koop had another commitment today, so Dr. Faye G. Abdellah, Deputy Surgeon General and Chief Nurse of the Public Health Service, will accept the medal for him.

Ms. Johnson: On behalf of the students and teachers will you please convey our thanks to Dr. Koop for his support of the Centennial celebration, for his interest in students everywhere, and for taking time from his busy schedule to spend an evening with us at the award ceremony at the National Academy of Sciences last winter.

Dr. Abdellah: Thank you, Ms. Johnson.

DR. WYNGAARDEN:

Thank you, Dr. Abdellah. Dr. William F. Raub, Deputy Director of NIH, will present a medal to Mr. Don Newman, Under Secretary for Health and Human Services. Accepting the medal in Mr. Newman's absence is Dr. Robert Windom, Assistant Secretary for Health.

Dr. Raub: We present this medal to Mr. Newman is recognition of his enthusiastic support of the programs and activities of the National Institutes of Health.

Dr. Windom: Thank you, Dr. Raub.

DR. WYNGAARDEN:

We do not have time before the outdoor ceremony to present medals individually to all who will receive them. However, Dr. J. Edward Rall, Deputy Director for Intramural Research, will present a medal to a representative of our international colleagues.

Dr. Rall will present a medal to Dr. Bengt Samuelsson of Sweden.

Dr. Samuelsson replies.

DR. WYNGAARDEN:

Thank you, Dr. Samuelsson. Dr. Katherine L. Bick, Deputy Director for Extramural Research and Training, will present a medal to a representative of the Underwriters Committee.

Dr. Bick: It is a pleasure to present this medal to Irwin Lerner, President and Chief Executive Officer of Hoffmann-LaRoche, who represents the entire Underwriters Committee, which has made this celebratory year possible. This medal cannot adequately express our deep appreciation of your faith in this biomedical enterprise and your demonstration of support for this institution.

Mr. Lerner replies.

DR. WYNGAARDEN:

Thank you, Mr. Lerner. And finally, it is my pleasure to ask Dr. Donald S. Fredrickson, my predecessor as Director of the National Institutes of Health, who has done so much for this institution, to accept this medal on behalf of the NIH Centennial Committee.

Dr. Fredrickson replies.

DR. WYNGAARDEN:

Thank you, Don, and thank you, one and all.

Mr. Flavin: And now we shall adjourn to the front steps of this building. Please take the elevator to the ground floor and use either side door. You will all be seated on the specially constructed platform in front of the stage. Our commemorative ceremony will start at 12:30. See you there!

A CENTURY OF SCIENCE FOR HEALTH*

by

James B. Wyngaarden, M.D.**

During the past six months we have told and retold details of the early, middle, and recent history of the National Institutes of Health. Today, in addressing the "Century of Science for Health," my remarks will be more in the nature of a commentary than a narrative. Using the framework of the history of the Institution as my outline, I will discuss some of the policies that have evolved in the past decades that have been responsible for the growth and development of this vital enterprise.

The mission of the Laboratory of Hygiene from which the NIH eventually materialized was limited. It was essentially a diagnostic adjunct to the quarantine station operated by the health authorities at the port of New York.

The national role of the Laboratory was confirmed when it was moved to Washington in 1891, but for the following 40 years it was small, having fewer than 200 total personnel until 1937. It was, however, uniquely effective in finding the cause and means of prevention of such serious problems as pellagra, psittacosis, tularemia, and Rocky Mountain spotted fever.

For the first 40 years of its history the principal goal of the Hygienic Laboratory was to find means for diminishing the fearful toll from infectious diseases.

Finally in 1930, with the passage of the Ransdell Act, the mission of the agency was restated making clear that all health concerns, not just the traditional public health responsibilities, were to be confronted by the

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*Opening address at the NIH Centennial Plenary Symposium, "Frontiers of Biomedical Research," in the Concert Hall of the Kennedy Center, Washington, D.C., October 17, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

agency. The Act described the NIH's principal responsibility to be "ascertaining the cause, prevention, and cure of disease." This broadened scope was reflected in the new name given in the legislation--the National Institute of Health.

Yesterday an impressive ceremony was held on the portico of the Shannon Building in exactly the same place where President Franklin D. Roosevelt in 1940 gave the dedicatory address for the original group of buildings on the new Bethesda campus.

In little over a year from the time he spoke, essentially all of the American scientific community had been mobilized in the war effort. Grants and contracts were awarded to American academic institutions, hospitals, and independent laboratories for the conduct of research on problems expected to be encountered by the armed services. Something over 500 awards were made during the war years. About 250 medical projects were still active when the Office of Scientific Research and Development was disbanded in 1945. The ongoing projects were turned over to the National Institute of Health for administration.

This was a turning point in our history. The action had a twofold meaning. For the first time approval was given to Federal support of biomedical research in non-government laboratories as an appropriate peacetime activity. Further, the action in effect designated the National Institute of Health as the principal biomedical research arm of the Federal Government.

The post-World War II period in the United States was a time of ebullient confidence that our Nation could accomplish any task, no matter how difficult, if it decided to do so. This climate of optimism was channelled by leaders in science and medicine as a driving force for the establishment of the modern NIH.

Extramural NIH was a new thing. No patterns existed for it; but in little more than a year after the passage of the authorizing legislation, a system was set in place that has stood the test of time and has served as a

model for organizations over the world. This largely unsung accomplishment was substantially the work of C. J. Van Slyke, then Chief of the Research Grants Division. His philosophy regarding the research grant program was a complete acceptance of the basic tenet that such a system should protect the integrity and the independence of the research worker and his freedom from control, direction, regimentation and outside interference. He insisted that the supported projects be selected in open competition, relying heavily on the appraisals of non-Federal scientists. In this manner the system was designed to use the expertise of scientists throughout the land, both in the conception and conduct of the research, and in the evaluation of research proposals.

It was vital to the future of NIH in its period of formative growth that there be a farsighted leader such as James Shannon, who understood that eventual success in the conquest of disease depended first upon a great expansion of knowledge of biological systems, on an army of well-trained scientists, and on a strengthening of the institutions where the bulk of research and training would be done.

Shannon showed unusual political skill in dealing with the Congress. He understood their point of view, and probably because of that he was able to convince key members that if we were to succeed in making substantial progress against disease and disability we must build upon an ever growing fund of basic knowledge. He maintained a special relationship with John Fogarty and Lister Hill that was a source of great strength to the NIH.

When James Shannon became Director in 1955, the intramural programs of the NIH were in a period of rapid growth. The Clinical Center had been opened in 1953 and staffing of the intramural laboratories for both basic and clinical research was proceeding. Some of the Shannon miracles were wrought in the early 1950s, when he was Scientific Director of the Heart Institute. He was able to recruit a young and talented cadre of investigators to the Heart Institute, including Chris Aneinson, Bernard Brodie, Sid Udenfriend, and Julius Axelrod. Don Fredrickson and I were both appointed by Jim Shannon as Research Associates in the Heart Institute in 1951.

Shannon presided over the NIH during a period of phenomenal budget growth, from $82 million in 1955 to $1.2 billion in 1968, an average increase of 24 percent per year.

When he first became Director it was clear to him that existing institutional facilities and personnel resources at grantee institutions would not suffice. He strongly advocated and nurtured programs for the construction of research facilities in academic centers. He also saw the critical need for biomedical research training programs within existing medical centers and graduate schools.

One of the things not often mentioned as an achievement of the NIH is the transformation that our programs brought about in American universities. The cumulative effect has been particularly marked in the area of the biological sciences. This came about through the infusion of scientists trained in the intramural programs of the NIH in both basic and clinical research, through rapidly increasing levels of funding of research, of training, and of facilities, and through the resultant additions in faculty with orientation toward research.

By the late 1960s events outside the sphere of biomedical research began to have an effect on the programs of the NIH. The Vietnam war's impact on the Federal budget was reflected in the NIH appropriation when in 1968, for one of the few times in the agency's history, the Congress appropriated a smaller amount than it had for the previous year. That was the year Jim Shannon retired and Bob Marsden became Director.

At about the same time and after almost two decades of debate the Congress began a variety of programs for the direct support of medical schools and other health professional academic institutions. The new Bureau of Health Manpower Education was assigned to the NIH, where it remained for five years. Its budget, more than $400 million, was larger than that of any other component of the NIH. In fact, it was more than the combined total of the two largest Institutes.

The National Library of Medicine also became a part of NIH in 1968.

Thus Robert Marston's directorship included the challenge of assimilating the Health Manpower Bureau and the Library, and facing the problem of maintaining stability in the grants program while operating with a reduction in funds. He formed a highly effective triumvirate with John Sherman and Robert Berliner that coped effectively with the changes and new responsibilities. There was a strong movement in the Congress to increase support for cancer research and to separate the National Cancer Institute from the NIH. Funding for cancer was greatly increased but the NCI remained with NIH.

During these years Congressman Paul Rogers and Senator Warren Magnuson exercised strong and constructive influence on our behalf.

A new set of issues challenged Robert Stone as Director in 1972. The total research budget of the NIH reached $2 billion in the second year of his tenure, and the very size of the agency's budget brought with it more attention than the NIH had previously enjoyed. With this attention came efforts to bring the relatively sheltered operation into the mainstream of the bureaucracy. There were efforts to shift the emphasis of NIH toward targeted research and to terminate Federal support for research training. Dr. Stone exerted himself successfully to resist these efforts and to protect the independence that had been so important to our sound growth.

One of the substantial contributions that Donald S. Fredrickson made as Director during his tenure--1975-1981--was through his masterful leadership in developing guidelines for safety in the use of the newly discovered recombinant DNA techniques. His efforts were successful in allaying fear with the result that restrictive legislation was sidetracked and the progress of some of the most important research of the century was not impeded.

Dr. Fredrickson also advocated attention to technology transfer as an NIH responsibility and in doing so defined more clearly the boundaries of the mission of NIH. Creation of the Office of Medical Applications of Research and the institution of consensus development conferences became a clear expression of NIH concern about health as well as science.

During the years I have been privileged to serve as Director, the extramural community has been particularly active in the support of NIH. Our congressional friends of long-standing, with the backing of the extramural community, have supported our appropriations so that we have experienced a 70 percent increase in five years--that is a real growth rate of 6 percent per year. The total number of research project grants has increased from 13,000 to 18,000. We now support 52,000 scientists in 1650 institutions in the U.S. and abroad; 1.5 percent of total budget is in international work. Main challenges apart from budget are animal issues and AIDS. Any current roll of congressional advocates of NIH must include the names of Weicker, Hatfield, Chiles, Natcher, Early, Conti and Obey.

There has been a marked increase in recent years in the portion of the budget going to investigator-initiated project grants, so that currently well over one-half of the total NIH budget goes to such awards. Furthermore, the preponderance of investigator-initiated research has had the effect of increasing the amount of basic research supported by the NIH.

While we have made a special effort to create more stability in funding for the benefit of extramural investigators, we have also given attention to reducing the administrative burden--the so-called bureaucratic accretion that tends to grow in the administration of review and approval processes. We are attempting to simplify the application process, to lengthen the time of awards, especially for outstanding mid-career scientists, and to reduce the extent of central direction of the research enterprise.

Our ability to carry out certain desirable practices in administration of our grant programs is limited at times by factors not totally within our control. For example, we cannot assure full funding of grants when we are required to make a specified number of new and competing renewal grants within a given appropriation.

As we stand at the end of the first hundred years of the new era in American science in which the NIH is such a major player, we have in field

after field the benefit of new insights that have been made possible by the extraordinary power of continuously refined methods and instrumentation.

Such advances will lead to new strategies for preservation of health, for disease prevention, for improved diagnosis, and earlier, more effective therapy.

We can predict with confidence that continuing progress will lead to new products for the benefit of mankind, some far outside the traditional perimeters of medicine.

Perhaps as important as these benefits, our gains in knowledge will enrich our understanding of ourselves.

The next century will be far more than a continuation of the current level of excitement. It can bring unimagined discoveries--advances that will enable the control of one after another of the presently intractable problems of health.

With great gains in knowledge will come attendant gains in power. We are challenged to wield with wisdom the application of the fruits of discovery.

TALKING POINTS*
BY
JAMES B. WYNGAARDEN, M.D.**

- I am delighted that I was able to accept Dr. Goldstein's invitation to be here this evening to participate in the University of Michigan's observance of the NIH Centennial.

- I would like to reflect on the history of the NIH and the challenges we face today and for the future.

- The Laboratory of Hygiene, the forerunner of the NIH, was established in 1887 on Staten Island for purely practical reasons: to help combat the major problems confronting public health officials at the time: yellow fever, cholera, and other infectious diseases believed to be entering New York Harbor along with immigrants. Although the mission of the laboratory was limited, this undertaking was supremely important for the Nation, because the laboratory from the start based its efforts on the new science of bacteriology just blossoming in the premier laboratories in Europe...those of Koch and Pasteur.

- In 1891 the Laboratory was moved to Washington, D.C., firmly establishing it as a national resource. It was uniquely effective in finding the causes and means of prevention of such serious problems as Rocky Mountain spotted fever, pellagra, tularemia, and psittacosis.

- In 1930, with the passage of the Ransdell Act, the mission of the agency was restated making clear that all health concerns, not just the traditional public health responsibilities, were to be confronted by the agency. The broadened scope was reflected in the new name, the National Institute of Health.

- World War II signalled the era of the "modern" NIH--the formation of strong partnerships with the University of Michigan and other academic institutions around the country.

- Following the war, some 250 war-related medical research projects underway in universities and hospitals were transferred to the NIH portfolio. The high-level decision to transfer the grants to the NIH confirmed our role as the principal biomedical research arm of the Federal government. It also established grants as a powerful mechanism for the support of such research.

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*Participation in the University of Michigan Celebration of the Centennial of the National Institutes of Health, Ann Arbor, Michigan, October 21, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

0 Recently, I learned of an interesting anecdote of this timeframe. Many of the projects transferred to NIH involved research on penicillin, and, when the price of the drug fell drastically late in 1945, NIH used the extra money to expand its grant program. The NIH director, Rolla Dyer, mailed what one historian called, "the most naive letter ever to have emanated from Washington." It was sent to the deans of all American medical schools and read, "We have limited funds available for research purposes. If you have investigators who need these funds, let us hear by return mail." "The freshet", wrote the historian, "became a flood", as academia gladly joined the partnership with government.

0 The post-World War II period in the United States was a time of ebullient confidence that our Nation could accomplish any task, no matter how difficult, if it decided to do so. This climate of optimism was channelled by leaders in science and medicine as a driving force for the establishment of the modern NIH.

0 There were some skeptics, however, who feared that government involvement in research might spell the demise of innovative, creative research in biomedicine...that government would support only targeted research with predictable outcome. Extramural NIH was a new thing. No pattern existed for it.

0 But in a little more than a year after the passage of the authorizing legislation, a system was set in place that has stood the test of time and has served as a model for organizations all over the world.

0 This largely unsung accomplishment was substantially the work of C.J. Van Slyke, then chief of the Research Grants Division, who in 1946 published a paper in Science magazine affirming NIH's complete acceptance of a basic tenet upon which the scientific method rests: The integrity and independence of the research worker and his freedom from control, direction, regimentation, and outside interference. He insisted that the supported projects be selected in open competition, relying heavily on the appraisals of non-Federal scientists. In this manner the system was designed to use the expertise of scientists throughout the land, both in the conception and conduct of the research, and in the evaluation of research proposals.

0 It was vital to the future of NIH in its period of formative growth that there be a farsighted leader such as James Shannon, who understood that eventual success in the conquest of disease depended first upon a great expansion of knowledge of biological systems, on an army of well-trained scientists, and on a strengthening of the institutions where the bulk of research and training would be done.

0 Shannon showed unusual political skill in dealing with the Congress. He understood their point of view, and probably because of that he was able to convince key members that if we were to succeed in making substantial progress against disease and disability we must build upon an ever growing fund of basic knowledge. He maintained a special relationship with John Fogarty and Lister Hill that was a source of great strength to the NIH.

- When James Shannon became Director in 1955, the intramural programs of the NIH were in a period of rapid growth. The Clinical Center had been opened in 1953 and staffing of the intramural laboratories for both basic and clinical research was proceeding. Some of the Shannon miracles were wrought in the early 1950s, when he was Scientific Director of the Heart Institute. He was able to recruit by fair means and bureaucratic sleight of hand a young and talented cadre of investigators, some of whom are still at NIH. Two of them, both graduates of the University of Michigan School of Medicine, later became NIH Directors.

- Shannon presided over the NIH during a period of phenomenal budget growth, from $82 million in 1955 to $1.2 billion in 1968, an average increase of 24 percent per year.

- When he first became Director it was clear to him that existing institutional facilities and personnel resources at grantee institutions would not suffice. He strongly advocated and nurtured programs for the construction of research facilities in academic medical centers. He also saw the critical need for research training programs within existing medical centers.

- One of the things not often mentioned as an achievement of the NIH is the transformation that our programs brought about in American universities. The cumulative effect has been particularly marked in the area of the biological sciences. This came about through the infusion of scientists trained in the intramural programs of the NIH in both basic and clinical research, through rapidly increasing levels of funding of research and of facilities, and through the resultant additions in faculty with orientation toward research.

- By the late 1960s events outside the sphere of biomedical research began to have an effect on the programs of the NIH. The Vietnam War's impact on the Federal budget was reflected in the NIH appropriation when in 1968, for one of the few times in the agency's history, the Congress appropriated a smaller amount than it had for the previous year.

- At about the same time and after almost two decades of debate, the Congress began a variety of programs for the direct support of medical schools and other health professional academic institutions. The new Bureau of Health Manpower Education was assigned to the NIH where it remained for five years. Its budget, more than $400 million, was larger than that of any other component of the NIH. In fact, it was more than the combined total of the two largest institutes.

- Robert Marston's directorship that began in 1968 was occupied with the challenge of assimilating the Bureau and the National Library of Medicine, and facing the problem of maintaining stability in the grants program while operating with a reduction in funds. There was a strong movement in the Congress to increase support for cancer research and to separate the National Cancer Institute from the NIH. Funding for cancer was increased, but the NCI remained within the NIH.

- A new set of issues challenged Robert Stone as director. The total research budget of the NIH reached two billion dollars in the second year of his tenure, and the very size of the agency's budget brought with it more attention than NIH had previously experienced. With this attention came efforts to bring the relatively sheltered operation into the mainstream of the bureaucracy. There were efforts to shift the emphasis of NIH to targeted research and to terminate Federal support for research training. Dr. Stone exerted himself successfully to protect the independence that had been so important to our sound growth.

- One of the substantial contributions that Donald Fredrickson made as Director was through his masterful leadership in developing guidelines for safety in the use of the newly discovered recombinant DNA techniques. His efforts were successful in allaying fear with the result that restrictive legislation was sidetracked and the progress of some of the most important research of the century was not impeded.

- Dr. Fredrickson advocated attention to technology transfer as an NIH responsibility and in doing so defined more clearly the boundaries of the mission of NIH. Creation of the Office of Medical Applications of Research and the institution of the consensus development conferences became a clear expression of NIH concern about health as well as about science.

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- There has been a marked increase in recent years in the portion of the budget going to investigator-initiated project grants, so that currently well over half of the total NIH budget goes to such awards. Furthermore, the preponderance of invetigator-initiated research has had the effect of increasing the amount of basic research supported by the NIH.

- While we have made a special effort to create more stability in funding for the benefit of extramural investigators, we have also given attention to reducing the administrative burden--the so-called bureaucratic accretion that tends to grow in the administration of review and approval processes. We are attempting to simplify the application process, to lengthen the time of awards to foster increased productivity and creativity, and to reduce the extent of central management of the research enterprise.

- Our ability to carry out certain desirable practices in administration of our grant programs is limited at times by factors not totally within our control. For example, we cannot assure full funding of grants when we are required to make a specified number of new and competing renewal grants within a given appropriation.

0 We have also made efforts to revitalize institutional training grant programs, encouraging longer periods of research training so that trainees can compete more successfully for grants in the future.

0 Although this about brings NIH history fully up to the present, major challenges for the NIH and the whole biomedical research community still stand. Among them are:

o combating the continued threat against medical progress brought by animal rights zealots who seek to stop all research involving animals.

o organizing our massive and complex efforts against AIDS.

o determining the relative emphasis to place on "little science"--that is research project grants--versus "big science"--that is larger, multidisciplinary efforts such as might be required to map and sequence the human genome.

o finding sensible ways of dealing with pressures to create new administrative units--such as new Institutes--within the NIH.

o continuing to find means to meet the equipment and instrumentation needs of academic research centers.

o defining the problem of decay of research facilities around the country and finding ways to remedy the situation.

o and finally, meeting the special needs of pressing health problems such as AIDS and Alzheimer's disease--which may require multidisciplinary center approaches--yet still support a necessary level of fundamental, investigator-initiated research.

REMARKS*

by

James B. Wyngaarden, M.D.**

I regret that it was not possible for me to be present this morning at the beginning of this conference, although I am certain that from Bill Raub's welcome you know how pleased we are that this meeting is taking place at the NIH.

It is interesting to speculate on how the NIH would have regarded such a meeting 20 years ago. It is likely that if an official of NIH had spoken of the agency's role with respect to biotechnology at that time, such remarks would have been considered inappropriate or at best speculative. Yet, at that time, much of the science base on which the new technology depends had been or was being discovered in the course of customary research activities.

While many exciting advances are being made in biotechnology today, it is not a new phenomenon. The history of modern biotechnology goes back at least a hundred years when Louis Pasteur was engaged in research that changed profoundly the course of the biosciences and medicine. Industry was a direct object of a substantial part of Pasteur's work. In addition to his development and first use of vaccines for rabies and anthrax, he is credited with saving the wine, beer and silk industries of France through his research.

For its part, the NIH would be enthusiastic about the concepts and methodologies of the science base supporting biotechnology, even in the absence of the commercial promise. For this new science has advanced our understanding of biological mechanisms and processes in health and disease

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*Presented at the National Conference on Collaborative Initiatives in Biotechnology reception at the Cloisters, Bethesda, Maryland, November 2, 1987.

**Director, National Institutes of Health, Bethesda, Maryland.

in ways that are unprecedented. Now, thanks to laboratory techniques such techniques such as recombinant DNA, we are beginning to make headway toward effective vaccine development in several recalcitrant fields. This is but one example. Biotechnology has had an impact on the conduct of basic biomedical research, comparable perhaps to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology, clinical immunology and the allergic response, and bone development and repair, just to name a few areas.

The NIH continues to make a major commitment to the future of biotechnology. The proportion of the NIH budget devoted to biotechnology has remained essentially constant for the past five years, with about 11 percent devoted to directly related research, and another 25 percent devoted to underlying basic research and research training.

When we think of the reasons for conducting biomedical research, it is obvious that the improvement of human health constitutes a complete justification. Within this generation, another reason has come into prominence--biomedical research as a foundation for biotechnology. With this new opportunity new challenges have emerged. It is good that those of us who are engaged in the different facets of this technology can meet and explore together ways in which we can maximize our collaboration.

# # #

BIOMEDICAL RESEARCH, HEALTH CARE AND THE COMPUTER*

by

James B. Wyngaarden, M.D.**

In his annual report for 1888 Surgeon General John B. Hamilton told of the establishment of a bacteriological laboratory in the port of New York. That laboratory, by the way, was the ancestor of the National Institutes of Health, but the primary reason for my mentioning it today is to point out the interest in equipment and instrumentation that existed at that time. The Surgeon General wrote that "the different apparatus supplied was modeled after those used in the laboratory of Dr. Koch of the Imperial German Health Board, and is supplied with Zeiss's latest improved microscope objectives and microphotographic apparatus....Additions have been made from time to time," he said, "until a very complete plant of apparatus exists for analyses and bacteriological investigations."[1]

The microscope became the accepted graphic symbol for biomedical research and continues to be widely employed as such. As recently as two years ago, when we were deciding upon a logo for the NIH Centennial, we elected to use a microscope to convey symbolically the nature and function of health-related research. However, if one were to be realistic and portray the instrument now used almost universally in biomedical research, the symbol would probably be a computer--certainly a computer is more typical of the laboratory today than the microscope.

And this is a relatively recent development. Although scientists have not been hesitant about using new laboratory equipment, it was not until the early 1960s that computers began to be seen by investigators as desirable or useful tools for biomedical research.

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*Keynote address at the 11th Annual Symposium on Computer Applications in Medical Care, Washington, D.C., November 3, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

Today, virtually every scientist can make some good use of computers. They are considered essential in practically every facet of basic biomedical research, from the synthesis of antiviral agents to sequencing the human genome. Computers also make it possible to create, store and retrieve the enormous and growing scientific literature.

Similarly, ready access to current medical literature helps the busy practitioner keep abreast of the explosive growth of new medical knowledge. Sophisticated computers are at the heart of such powerful diagnostic tools as computer assisted tomography, positron emission tomography, and magnetic resonance imaging.

The Computer as a Laboratory Instrument

A substantial amount of the change that has taken place can be traced to a computer developed by an MIT engineer, with support from the NIH. Acting on his belief that a computer should be just another piece of laboratory equipment, Wesley Clark decided to build a computer that researchers could control easily. He also wanted the computer to be inexpensive (no more than $25,000) and physically compact--"low enough to see over," he said. He also believed that the machine should not intimidate its user. With these specifications in mind he built a prototype laboratory instrument computer, and dubbed it LINC to acknowledge MIT's Lincoln Lab where he worked and to symbolize the function of linking the user to his machine. The LINC was a precursor of the minicomputer.

Dr. Edward David, former science advisor to the President, told an audience at an NIH celebration of LINC's twentieth anniversary in 1983 that "To understand why LINC was such a discontinuous leap, we must also remember that in the early 1960s biomedical researchers were about the last on the totem pole of computer users. And the available IBM mainframes could be adapted to signal processing problems only with duress. Moreover, when access was possible, scientists still had to wait hours or days before they could see whether the data had been entered and processed correctly, let alone begin to study the results. As a consequence, few biomedical researchers availed themselves of computing technology."[2]

In the medical research laboratories of the early 1960s, computers were untouchable megaliths enclosed in immense glassed-in sanctuaries guarded by enormous DO NOT ENTER signs and accessible only to computer professionals. The costs of using these digital computers were prohibitive--$100 or more an hour--and these computer systems were unsuited for most laboratory uses. Furthermore, research scientists needed something to help them design and control laboratory experiments, not just to analyze vast amounts of data.

Computing at NIH began with the establishment in 1954 of a small, central, punched card processing facility in the Office of the Director. The facility primarily was used for work in the biometrics. In 1958 NIH got its first digital computer.

During the early 1960s the demand for computer services increased. In May 1962 NIH Director James A. Shannon appointed a steering committee to examine and evaluate NIH's automatic data processing needs for the present and the future. The committee concluded from its year-long study that NIH needed to broaden its commitment in computing from just providing ADP services. The committee recommended the establishment of a Division of Computer and Information Sciences, incorporating expertise in mathematics and computer science.

In April 1965 the Division of Computer Research and Technology (DCRT) was created. The Division has primary responsibility for incorporating the power of modern computers into the biomedical programs and administrative procedures of NIH. It also serves as a scientific and technical resource for other parts of the U.S. Public Health Service, and for other Federal organizations with biomedical and statiscal computing needs. Much of the credit for the sound and imaginative development of DCRT is due its Director, Dr. Arnold W. Pratt, who after 21 years continues to give strong leadership to the Division. The DCRT has been an indispensible resource for the NIH as our interest in computing has grown stronger and as we have adapted to continuing changes in both biomedical research and computer technology. Now there are growing centers of computing experience throughout the NIH's Bureaus, Institutes and Divisions.

Molecular Biology and the Computer

Today, molecular biology is at the forefront of the scientific enterprise and DCRT is actively engaged on this front. The ability of computers to transform static descriptions of large molecules into dynamic three-dimensional images allows scientists to see and explore interactively the structure of biological molecules at a level unparalleled in science before.

The computer graphics revolution is a significant development, allowing scientists to compile and compare substantial amounts of data on the structure of proteins and other biological building blocks.

In addition, computers are used to model molecules mathematically and to explore graphically viruses, membranes, and other subcellular structures in order to understand more fully how structure relates to function in health and disease.

DCRT scientists are now developing and using computer technology to solve some of biomedicine's most complex physical and chemical problems.

"Molecular engineers" with the use of computer graphics are discovering how to alter and conceivably to improve protein design.

In the past five years much of the activity in molecular graphics has been devoted to modeling proteins by extending the results of x-ray crystallography. It has become clear that proteins exist in families and super families that share similar amino acid sequences and folding architecture. The similarities of architecture have formed the basis of graphic modeling.

The approach combines mathematics and computer science with biomedical expertise, using advanced computer equipment and software.

Scientists from across the Nation and around the world make use of NIH's powerful computer system for modeling molecules. These molecular graphics tools have been useful in our current AIDS research. With such

tools, we can see the three-dimensional structure determination of selected portions of surface glycoproteins as we continue the effort to develop an antiviral agent for AIDS.

Our scientists are also working to develop a way to build protein models by folding the primary protein sequence, utilizing basic knowledge. The achievement of this goal is still some years in the future but significant steps have been made toward its fulfillment.

Computers as Information Resources

In addition to their essential functions in connection with specialized data bases and graphics, computers have made possible the development of an invaluable information resource for biomedical research, medical education and the practice of medicine through various programs of the National Library of Medicine.

Keeping track of the ever-growing mass of published medical and scientific information would be impossible were it not for the cataloguing and indexing done by the National Library of Medicine. Some 300,000 references each year are entered in the NLM's computerized database, called MEDLARS, and published in the monthly Index Medicus. Before the advent of online bibliographic searching, inquiries of the NLM's database depended upon the mail for requests and return of requested material. With a turnaround time of several weeks, NLM could handle only about 20,000 such requests a year.

Then in October 1971, MEDLINE was created to provide online bibliographic search of MEDLARS, and it became an instant success with medical librarians at some 25 institutions. Today, it is a nationwide network of centers at more than 5,800 universities, medical schools, hospitals, government agencies and commercial organizations. Librarians at these institutions now conduct close to four million MEDLINE searches each year.

The growth of personal computing has led to an increase of individual rather than just institutional users of MEDLINE. The Library has developed GRATEFUL MED, a user-friendly system to accommodate even more such users.

The National Cancer Institute, jointly with the National Library of Medicine, operates the Physicians Data Query (PDQ) communications system that can provide physicians with information about the protocols for a large number of clinical trials currently under way. The system makes it possible for a physician with a personal computer to gain access to a central computer at the NLM and to identify protocols for which certain of their patients may be eligible. The protocols may present new approaches for application by the inquiring physician, or give the physician the names of physicians and hospitals in the area that are participating in clinical trials that may offer opportunity for referral.

PDQ provides state-or-the-art cancer treatment and referral information, unique in that it is a comprehensive information resource covering an entire clinical specialty. Its monthly updates allow physicians to keep abreast of the most advanced treatments. Although the information in PDQ exists in other places, the physician may gain access to it more rapidly and conveniently with PDQ.

The NIH's Division of Research Resources has provided funding for a number of different kinds of biomedical technology resources. In so doing it has contributed to the solution of important biomedical research problems. The DRR-supported biomedical research technology resource centers take many forms such as biomedical computer centers, biomedical engineering centers and instrumentation centers for study of biomolecular and cellular structure and function. The centers serve research investigators locally within the grantee universities, as well as regionally and in some instances nationally. Currently 21 centers scattered throughout the Nation are designated as Computer Resources. At this time the DRR is providing over $20 million per year for the support of the computer resources.

Artificial Intelligence

About 15 years ago the DRR awarded Stanford University funds to begin studies of the application of artificial intelligence to medical and biomedical problems. The principal investigator at the time of the first award under this program was Nobelist Joshua Lederberg. We have frequent reminders of the continued productivity of the joint activities of the

Departments of Medicine and Computer Science at Stanford through publications in various journals of papers from the Medical Computer Science Group, on such subjects as computer programs to support clinical decision making.

The Lister Hill National Center for Biomedical Communications, a part of the National Library of Medicine, since 1985 has also conducted a research program in artificial intelligence, concentrating on computer programs that combine knowledge of a particular subject area with inferencing mechanisms, enabling their use in problem solving. Such systems are intended to assure the accessibility of specialist level expertise by making it available in the classroom and in the clinic when human experts are not.

Dr. Donald A. Lindberg, who became Director of the National Library of Medicine in 1984, is a leader in the application of information science to biomedical research and medical care. He established one of the Nation's first medical computer centers at the University of Missouri in 1963. Some of the artificial intelligence systems under development at the Lister Hill Center are extensions of work initiated by Dr. Lindberg. An example is the system designated AI/RHEUM for diagnosis and therapy recommendations in rheumatology. It is unusual among expert systems in offering the user direct access to information from four knowledge sources: text definitions, videodisc images, the disease criteria tables that are the foundation of its medical knowledge base, and direct access to NLM's MEDLARS family of data bases.

A moment ago I mentioned publications from Stanford's Medical Science Computer Group. In a recent article, published in the October SCIENTIFIC AMERICAN, Glenn D. Rennels and Edward H. Shortliffe commented on the application of Advanced Computing for Medicine. One of their statements is in the nature of a caveat about the process that should disarm some of the more traditionally oriented criticisms of the use of computers as advisors. They noted, "Computer systems do not now--nor will they soon--have a sufficiently complete understanding of medicine's technical, clinical and social considerations to approach the richness and flexibility of human expertise. The advice systems represent advances in medical computer

science, but none of them is effective without the common sense and judgement of an experienced health care worker. There are many aspects of human problem solving that we and others in the field simply do not yet know how to model within a computer."[3]

Computers in Health Care

Let me turn now to some direct applications of computer capability to problems of diagnosis and treatment. Just as the computer has become ubiquitous in the laboratory it is a presence in practically every aspect of clinical care. Not only is the computer the essential element of many of the non-invasive diagnostic instruments, it performs at every level of sophistication to enhance the effectiveness of the clinician and the medical care institution. For example, as late as the mid-1970s the only way to watch the living heart in action involved catheterization and the use of x-ray. It was then that the work of a physician, an engineer, a computer programmer, and a physicist at the NIH led to a better way to take "pictures" of the working heart.

They created a new diagnostic procedure that combined the latest in minicomputer technology with the "gamma camera," a device capable of imaging radiation emitted from within the body. With this camera positioned over the patient's heart, a very small amount of radioactivity was injected into the blood stream where it circulated continuously. The radiation emitted by blood in and around the chambers of the heart was collected by the camera in synchrony with the patient's electrocardiogram during 1,200 to 1,600 heartbeats. These data were then transferred from the minicomputer system to a large digital computer that organized the radioactive emissions into a series of 80 to 100 "time frames." Each represented a small time segment in an "average" heart beat cycle. The final product, a computer generated "movie" of the working heart, revealed the heart's size, shape and how well the chambers of the heart were pumping blood. This research procedure was then put entirely on the minicomputer, thereby making it clinically practical. Poorly contracting heart muscle, enlargement of the heart, and other changes often associated with heart disease could be detected from outside the body.

The technique was used to study patients with heart disease during rest and vigorous exercise. It caused no discomfort to the patient and no more radiation exposure than from a single chest x-ray. Thus radionuclide ventriculography rapidly became an important diagnostic tool in U.S. hospitals.

The Human Genome Project

The complexity and size of biotechnology information astound the imagination and make it different from other scientific information. And this information is growing today at an amazing rate.

The rapidly increasing sophistication and capacity of computers makes it possible for scientists to give serious consideration to proposals to characterize the entire human complement of genes--the human genome. A decade ago this project would have been considered by many to be a bit of science fiction. But the fact is that the technology for accomplishing it exists today.

There is general enthusiasm for proceeding. We are driven by curiosity, to be sure, but also by the belief that the secrets of the genes will greatly enlighten our quest for new insights about developmental biology, cellular regulation, and disease mechanism.

Consider, for example, that 4,000 human diseases have a genetic basis, including cystic fibrosis, Duchenne-type muscular dystrophy, Huntington's disease, and Alzheimer's disease. Such a project could result in discovery as to why some persons get diseases such as cancer, heart disease, and mental illness, and others do not. Furthermore, such a project would provide an exponential increase in the knowledge of human biology.

The most pressing problem is to devise means for dealing with the vast amount of data that will be generated by the genome project.

Tens of thousands of individual human genes control our life processes. Three billion units of DNA make up the totality of human genes, or the human genome, and less than half of one percent of them have been sequenced.

With current technology, sequencing these three billion units could consume 30,000 persons-years and upward of $2 billion. Fortunately technology is continuously improved.

Technical advances--including ways to separate large molecules and individual chromosomes--have upped the rate of analysis about ten times in the last decade. A molecular biologist in a technically advanced laboratory today can sequence about 300 DNA units a day. Recent development of an automatic sequencing machine that speeds sequencing tenfold promises to cut the cost for each base in half, from one dollar to fifty cents.

All this effort, all this information would be useless without computerization. As information has poured out of the laboratories factual data bases have been developed to store it.

Databases established to handle DNA sequence information have been swamped. GenBank, which is the principal United States' database, was planned and launched by the NIH's National Institute of General Medical Sciences. It is funded as an interagency project, involving the Departments of Energy and Defense and the National Science Foundation, as well as four components of the NIH. GenBank is located at the Los Alamos National Laboratory. The European Molecular Biology Laboratory (EMBL) at Heidelberg established a DNA database in 1980. Formal collaborative arrangements were established between GenBank and EMBL in 1982.

The challenge to these databases is in the extremely rapid growth of the rate of publication--from one sequence composed of 76 bases in 1965 to a total of 14,000 sequences composed of 14,000,000 bases as of October this year. These numbers are expected to increase by twentyfold to fiftyfold in the next five years.

In addition to the problem of sheer volume of data is the difficulty created through different databases using different information systems--different computer languages, and these have resulted in a veritable Tower of Babel. One approach to avoiding the impediments that could result from overloads to the system has been advanced in the form of legislation to

create a National Biotechnological Information Center at the National Library of Medicine.

Working with the laboratories from which information comes, experts at such a center would seek to coordinate data as it is accumulated--to store, process and make it available to the research community, nationwide.

Developing such a national center would, of course, prevent duplication. It would enable scientists to work in a more collaborative style--conferring frequently to avoid reinventing the wheel. The center is needed to fit together the pieces of the genetic puzzle and acquire the knowledge that would benefit humankind in many ways.

With such knowledge, we could develop deeper understanding of the root causes of many disease problems, particularly the ones we know to be inherited.

The possibility of characterizing the human genome has brought us face to face with a question of science policy that has been encountered more frequently in physics, for example, than in the biosciences. It is the question of "little science" versus "big science." Would an all out effort to carry out this project be justified if its pursuit would jeopardize the support of traditional small science investigator-initiated research projects of unknown potential? We seek to find an accommodation that will permit us to pursue the genome without detracting from existing programs.

As the NIH enters its second century we can be sure that our ingenuity and judgement in the administration of scientific programs will be tested. New understanding of the potential of the computer in biomedical research will be required. Such matters as the review of grant applications containing a mixture of the biological and computer sciences will challenge us to use ever broader ranges of expertise in peer review.

In his intriguing volume "A Guided Tour of the Living Cell," Nobelist Christian De Duve reminded his readers of the crucial role of instruments and techniques in the progress of science. He then explained, "Not that

the creative faculties of intellect, intuition, imagination, sometimes even genius, may not be of crucial significance at some stage. But," he concluded, "these faculties are powerless without the means of establishing contact with reality."[4]

Computers by their nature dwell in the abstract world but paradoxically they are becoming increasingly powerful tools for establishing our contact with reality."[4]

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WELCOMING REMARKS AT SCIENCE COUNSELORS' DAY*

BY

JAMES B. WYNGAARDEN, M.D.**

I would like to welcome you here today on behalf of the National Institutes of Health in this, our Centennial year. Many of you have helped us to arrange Centennial events in your own countries, and I have been fortunate enough to attend a number of them. The NIH's alumni include distinguished scientists from all over the world, and we have all benefitted from their study and research here. An important part of obtaining knowlege is sharing it, and many of our foreign colleagues have become leaders in their home research communities after working here.

In a few minutes, Dr. Schmidt will give you an overview of the NIH and its international activities. I would like to tell you something about this remarkable institution on the occasion of its 100th anniversary and acknowledge the value of our international ties with so many nations.

The scientist and author, Lewis Thomas, has called the NIH "the most brilliant social invention of the 20th Century--anywhere." That is high praise indeed, and it reflects the fact that the National Institutes of Health has directly or indirectly improved the health and well-being of almost every man, woman and child in the United States and, indeed, throughout the world.

Let me first describe the NIH as it is today, then review some of its early history and accomplishments, and finally discuss some of the enormous challenges that lie ahead.

The National Institutes of Health is the principal agency of the Federal Government devoted to conducting and funding biomedical research. Its legislative charge is really quite simple--to uncover new knowledge of potential benefit to the health of the people. Our international component is a vital one at the NIH. Many of the world's leading scientists have received valuable training or have conducted research in their own biomedical specialties here. This is mutually beneficial. The visiting scientists learn our techniques and ideas in conducting research, and we benefit from their ideas and expertise. More than 1,500 scientists from 70 nations are currently participating in our visiting program. There are a number of other exchange programs, on which Dr. Schmidt will elaborate, for American and foreign scientists to conduct collaborative research both here and abroad.

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*Visit of Foreign Science Counselors, Wednesday, November 4, 1987, Stone House, NIH.

**Director, National Institutes of Health, Bethesda, Maryland.

As large as the intramural program is, however, the largest part of NIH research today takes place in some 1600 universities, medical schools, hospitals, independent and industrial laboratories across America. Last year the NIH funded more than 28,000 research and training projects involving approximately 50,000 non-federal scientists.

The key mechanism used by the NIH for support of biomedical research is the investigator-initiated project grant. Well over half of our total budget is allocated to such projects for the conduct of research by non-federal investigators. Such research draws upon the expertise and intuition of the American scientific community, and our peer review system has become a woldwide model.

The total budget of the National Institutes of Health in 1987 was over 6 billion dollars. That represents a 70 percent increase in just the past 5 years and 17 percent in the last year alone. We realize that an increase of this magnitude during a time of budget restraint is an indication of the level of confidence that exists in this country as to the long-term value of biomedical research.

I would like now to discuss a little bit of history and in rather broad brush strokes paint the development of the National Institutes of Health in its first 100 years. The early history of the NIH is closely intertwined with European science of the late nineteenth century. The 1880s and 1890s were years in which a rapid expansion of knowledge was opening new areas of human endeavor. It was also a time of solid scientific advances, particularly in chemistry, physics, and biology.

A yellow fever epidemic in 1878 created widespread alarm in the United States, and a variety of measures--none particularly effective--were proposed for prevention and control. Other communicable diseases were also causing serious concern. Health authorities feared that the cholera pandemic of 1881 might be imported from overseas, and they sent a young American doctor, Joseph Kinyoun, to Europe to study with the pioneers in microbiology. They hoped that new insights from their laboratories might provide ways to prevent a wave of cholera in the United States.

Upon his return, Dr. Kinyoun set up a bacteriological laboratory in 1887--called the Laboratory of Hygiene--in an attic room of the facility of the Marine Hospital Service on Staten Island, New York. The National Institutes of Health is the lineal descendant of that laboratory.

In 1891, the modest laboratory established by Dr. Kinyoun was moved to Washington and, over the years, provided the scientific support for scientists such as Howard Taylor Ricketts and Joseph Goldberger who solved such riddles as the cause of Rocky Mountain spotted fever and pellagra and provided the knowledge for preventing them.

In 1930, the Congress broadened the scope of responsibility of the institution to the virtually unlimited mission of "...ascertaining the cause, prevention and cure of disease." At that time the name "National Institute of Health" was given to the laboratory.

The modern era of the NIH--as well as of biomedical research in the United States--began when the government and non-government research laboratories joined their efforts in carrying out research during World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the armed services, the government turned to the established non-federal academic and independent laboratories for help in conducting vital research. Grants and contracts were awarded for the support of essential investigations. This arrangement worked well. These newly formed partnerships accelerated progress in research and development across the spectrum.

By the war's end, the U.S. Office of Scientific Research and Development--OSRD--was administering about 250 medically related research projects at universities, medical schools, hospitals, and pharmaceutical companies. The OSRD decided to turn over the government's administration of these projects to the National Institute of health. This decision confirmed the Institute's role as the principal biomedical research arm of the Federal Government. It also established government support of research in non-government institutions as the dominant mechanism for carrying out biomedical research. Later, as research continued to expand, the NIH became the National Institutes of Health.

Increases in the NIH budget became spectacular following the addition of the extramural dimension to its programs. Appropriations of the NIH grew at an astonishing average rate of 24 percent per year for more than 20 years between 1945 and 1968. This expansion of the NIH organization reflected public concern about specific diseases and general categories of health problems. Some of the buildings and centers at the NIH today are named for key congressional leaders whose vision and foresight turned the NIH into the world's largest biomedical research center. Lister HIll and John Fogarty are among those whose names will be linked forever to expanding science in order to conquer mankind's age-old enemy, disease.

The medical sciences have indeed made great strides throughout the world in the past 40 years. Fields such as genetics, virology, molecular biology, biochemistry and immunology have attracted the brightest and most productive investigators of our era. Discoveries have come so quickly that it is almost impossible to keep up with these highly specialized fields. Newly developed instrumentation has taken us from vacuum tubes to transistors to computer chips; from x-rays to CAT scans to position emission tomography and magnetic resonance imaging.

All this has permitted amazing advances in our fundamental understanding of human biology. In particular, scientific attention today is focused on the structural biology of organisms at the cellular and molecular level, and on the mechanisms by which they function properly or fail.

These are more than theoretical excursions. For example, earlier this year the NIH began a new program in the structural biology of the AIDS virus, in a special effort to understand this virus at the most minute level of structure possible and to develop new types of drugs against it.

Scientists at the NIH and elsewhere are also giving serious consideration to the wisdom of proposals to attempt to characterize the

entire three billion neucleotide human genome. A decade ago this project would have been considered in many quarters to be science fiction. But the fact is that the technology for accomplishing it exists today. In this effort, as well as in many others in basic science today, international cooperation is an essential element.

In recent years, a new justification for government support of research has come into prominence: biomedical research as a foundation for biotechnology. The Administration--and the Congress--have become interested in the economic consequences of our national investment in biomedical research that has been responsible for the emergence of biotechnology.

Biotechnology has had an impact on the conduct of basic biomedical research comparable to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology, clinical immunology and allergic response, and bone development and repair, to name just a few. And biotechnology has created an unprecedented set of opportunities, issues and concerns in which the NIH--and the peoples of the world--have a great interest.

This is our future priority: To build on the past century's accomplishments and search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability. This is truly universal, for as Disraeli said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."

Again, welcome to the National Institutes of Health. We always stand ready to cooperate with you and your countries' governments--and scientists--in meeting our common goals.

THE POLICIES AND PROGRAMS OF NIH: MYTHS, REALITIES, AND FUTURE DIRECTIONS

INTRODUCTION

o Good morning. Thank you for joining us today to discuss the impact of NIH policies and programs on the health of biomedical research institutions.

o Sitting at the table with me this morning are representatives of the NIH national advisory councils, members of the Advisory Committee to the Director, NIH, and senior NIH staff who will spend the remainder of the day receiving public testimony and participating in discussion. I would like to introduce:

[For Los Angeles Meeting]

o Dr. Katherine Bick
Deputy Director for Extramural Research

o Dr. Jerome Green
Director, Division of Research Grants

o Dr. Barbara Packard
Associate Director for Scientific Program Operation
National Heart, Lung, and Blood Institute; who is attending for Dr. Lenfant

- Dr. Betty Pickett
  Director, Division of Research Resources

- Dr. David Rall
  Director, National Institute of Environmental Health Sciences

- Dr. Carol Newton
  A member of the Advisory Committee to the Director, NIH

- Dr. Thomas Yarrington
  A member of the National Advisory Neurological and Communicative Disorders and Stroke Council

- Dr. Gerald Finerman
  A member of the National Arthritis and Musculoskeletal and Skin Diseases
  Advisory Council, and

- Dr. Norton Gilula
  A member of the National Advisory General Medical Sciences Council

- Dr. Doris A. Howe
  A member of the National Center for Nursing Research Advisory Council

[For San Francisco Meeting]

o Dr. Katherine Bick
Deputy Director for Extramural Research

o Dr. Jerome Green
Director, Division of Research Grants

o Dr. Barbara Packard
Associate Director for Scientific Program Operation
National Heart, Lung, and Blood Institute; who is attending for Dr. Lenfant

o Dr. Betty Pickett
Director, Division of Research Resources

o Dr. David Rall
Director, National Institute of Environmental Health Sciences

o Dr. John Bishop
A member of the Advisory Committee to the Director, NIH

o Dr. Carol Newton
Also a member of the Advisory Committee to the Director, NIH

- Dr. Robert Fishman
  A member of the National Advisory Neurological and Communicative Disorders and Stroke Council

- Dr. Gerald Finerman
  A member of the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council, and

- Dr. Norton Gilula
  A member of the National Advisory General Medical Sciences Council

- Dr. Dyanne S. Affonso
  A member of the National Center for Nursing Research Advisory Council

- As many of you may know, the NIH is concluding the observance of its 100th anniversary. The occasion has been marked by a year-long series of seminars, conferences, symposia, receptions, radio and television broadcasts, an NIH alumni reunion, and a variety of events held across the country, and abroad, to provide public recognition of the role of NIH in what has been described as "A Century of Science for Health."

- In reflecting on the rich history that has been achieved during this century of science, we take special pride in the successful partnership that was forged between the NIH and the universities and other biomedical research institutions. We are also reminded that a partnership such as ours--that is based on mutual dependence and trust--must be constantly nourished, and that this process can occur only if the lines of communication are open and clear.

- The NIH routinely strives to keep the scientific community informed of important new developments and anticipated actions and attempts to involve a broad segment of that community in decisions that have clear implications for universities and other research institutions.

- From time to time, however, the need may arise for a special, concerted effort to renew the dialogue and strengthen communications between the NIH and the constituents it serves, and to involve directly a representative cross-section of that constituency in planning the future course of biomedical research policy.

- It is toward that end that we are convening this series of regional meetings to examine the general characteristics and specific elements of the current Federal system of sponsored

research that are contributing to stability or instability of biomedical research institutions and influencing the quality, creativity, and scientific productivity of the biomedical research enterprise.

- My observations lead me to believe that it may be useful to preface this public forum with a few remarks concerning (1) the Federal budget process as it affects the formulation of the NIH budget, (2) recent trends in the funding of NIH programs, and (3) some aspects of broad strategies adopted by NIH to meet the perceived needs of biomedical research.

  - I say this because there appears to be a growing discrepancy between the facts concerning the policies, programs, and funding of the NIH, and the perceptions that have gained currency in the scientific community regarding such factors.

- It is not my intention to defend or "paper over" the problems and stresses that undoubtedly exist within the current system of support for biomedical research and training. I do, however, wish to dispel some of the myths and misconceptions that may be clouding perceptions and standing in the way of fruitful discussion so that we may better focus our deliberations on the true nature of the problems confronting us.

MYTHS

The NIH Budget

o As one travels across the campuses of this country and attends meetings of professional societies and voluntary health agencies, one of the most frequently heard comments is that the NIH appropriation has been slashed, that the Federal support of biomedical research is capricious, and that the future of biomedical research is uncertain.

oo That statement simply does not comport with the facts!!

o The overall growth rate of the NIH appropriation since the late 1960s has been two percent per year, even when factoring in the three brief intervals when the appropriation lost purchasing power for periods of two, one, and three years as shown in [SLIDE 1].

oo In only one of these years, 1970, did the actual appropriation decline from that of the previous year [SLIDE 2]. In all other years when purchasing power was lost, the explanation was inflation running ahead of the appropriation.

oo And--contrary to popular belief--recent NIH budgets have continued to grow in spite of the general climate of fiscal austerity.

oo In fact, one of the most satisfying aspects of my first five years as Director of NIH has been the sustained growth of the NIH appropriations, amounting to 70 percent in current dollars and 28 percent in real terms.

--In each of the last three years the NIH appropriation has set a new record in constant dollar terms.

--And, the Fiscal Year 1987 NIH appropriation of $6.18 billion represented a 17 percent increase over the FY1986 appropriation.

o Yet the view appears to persist that the NIH has not fared well in the budget process. I am convinced that this widely held view stems--at least in part--from the complex and somewhat arcane nature of the budget process. It is often difficult for most casual observers to follow the long and tortuous path leading to a final appropriation and, therefore, they may be left with partial and misleading impressions of how the "budget battle" has turned out each year. Consequently, I believe it might be useful at this point to provide a brief primer on the NIH appropriation process.

The NIH Appropriations Process

o It is important to understand not only the process by which the President's Budget request for NIH is developed within the

executive branch, but also the parallel process that takes place in the Congress.

oo The Senate Subcommittee on Health and Environment, chaired by Senator Kennedy, and the House Subcommittee on Health, chaired by Congressman Waxman, are the authorization committees for NIH programs. The authorization laws which originate from these committees have two functions -- they determine or "authorize" the types of activities NIH can legally perform and specify for some activities the maximum amounts of money that can be appropriated.

oo The Senate Budget Committee, chaired by Senator Chiles, and the House Budget Committee, chaired by Congressman Gray, initiate the Budget Resolutions that specify annual revenue and appropriations targets for the Congress. Although the Budget Committees may determine their overall targets by developing specific spending estimates for separate agencies such as NIH, these specific amounts are not binding and the final appropriations for NIH may be substantially different from the Budget Committee estimates.

oo The Senate Subcommittee on Appropriations for Labor/HHS, chaired by Senator Chiles, and the House Subcommittee on Appropriations for Labor/HHS, chaired by Congressman Natcher,

initiate appropriations bills for NIH. Unlike authorizations which set a ceiling for appropriations and budget resolutions which set targets for appropriations, appropriations determine the actual amounts that will be available to NIH to spend.

o Part of the difficulty involved in following the budget process is due to the length of the process and the overlapping multi-year functions carried out during this process. Since approximately 37 months are involved in the period from inception to final enactment of a budget, at any given time we may be working with budgets for three or four different fiscal years. For example, in October of 1987, we were closing out FY 1987, beginning execution of the FY 1988 budget, and completing the formulation phase of the FY 1989 budget. In addition, we were beginning the planning phase of the FY 1990 budget. [SLIDE 3]

oo The fact that we are planning a FY 1990 budget at a time when we are unsure what the actual budgets will be for FY 1988 and 1989 demonstrates the uncertain and fluid nature of the process. Obviously substantial changes can occur over this time in research advances, technological developments, and scientific directions and priorities.

oo This occurred recently, for instance, in the emergence of a critical need for additional research and development in AIDS. In some instances, these unanticipated needs are met through

budget amendments and supplemental funding. At other times, they must be absorbed or partially absorbed within existing resources.

oo Each step in the development of the budget involves a great deal of discussion, and sometimes disagreement, concerning future directions, priorities, and appropriate funding levels. This occurs first within the NIH, later with the Public Health Service, the Department of Health and Human Services, and then of course finally with the OMB. It is during these periods that the program managers, including the Director of NIH, have their opportunity to influence the development of the President's Budget.

oo The budget formulation process is iterative. This is an inherent trait due to fiscal changes in the base years, changes in scientific directions, and changes resulting from many different layers of review. Let me illustrate this by briefly outlining the development of the FY 1988 budget.

--During the late Fall and early Winter of 1985, I held planning and appropriation briefing sessions with each of the NIH Bureaus, Institutes, and Divisions. These discussions became the basis for the NIH FY 1988 Research Plan that described current research developments, areas of concern, new initiatives, and program changes.

--In the early Spring of 1986, the FY 1988 Research Plan served as the basis for the individual institute's development of their preliminary budget requests to NIH. These requests were reviewed and decisions were made by me, in collaboration with the institute directors, on program priorities and overall funding levels. The FY 1988 Preliminary Budget Request to the Public Health Service was then prepared and submitted in May of 1986.

--After a review of our budget at the PHS level, PHS issued preliminary budget recommendations. Following NIH appeals of these preliminary recommendations, the Assistant Secretary for Health determined the final budget amounts. These amounts for NIH were incorporated into the PHS budget which was submitted to the Department in June, where a second review, allowance and appeals process occurred. In September of 1986, the Department's budget was submitted to OMB.

--At each stage in the process, the NIH budget was revised to reflect the priorities expressed by officials at each level of review as well as changes in targeted spending levels. It should be noted that, the base for the FY 1988 request was an adjusted FY 1987 President's Budget. This base did not incorporate House or Senate action on the FY 1987 request.

--In late November 1986, NIH received the OMB's initial FY 1988 allowance. In the meantime, the FY 1987 Appropriations Act had passed which provided over $1 billion in additional funding. This action significantly increased the FY 1988 commitments. Because the OMB took into account the additional FY 1988 commitments generated from FY 1987 congressional action, the FY 1988 allowance differed substantially from the FY 1988 request.

--The OMB's FY 1988 allowance also proposed changes to the FY 1987 appropriated level. In order to decrease the amount of FY 1988 commitments and to provide for a more stable level of funding and a smoother transition between FYs 1986, 1987, and 1988, the allowance proposed to extend the availability of $334 million of FY 1987 grant funds into FY 1988. This proposal would have resulted in a decrease in the number and average costs of FY 1987 grants. The House and Senate, however, had rejected the FY 1987 extended availability proposal in the reports that accompanied their FY 1987 supplemental bills.

--After a process of appeals on the initial OMB allowance, the final OMB decisions were made and the FY 1988 President's Budget was prepared. It was submitted to the Congress in early January 1987, and in March, the Appropriations Committee hearings were held.

--During the hearings, it was my role as agency head, as well as the role of the Institute Directors, to defend and justify the Presidents budget. This is a traditional role that has not changed substantially over the years. It was described succinctly by President Truman in 1946 when he issued a memorandum that read:

> "I have noticed that on several occasions certain department and agency officials have shown a tendency to seek from Congress larger appropriations that were contemplated in official budget estimates . . . . While agency witnesses before congressional committees must feel free to supply facts in answer to questions of committee members, I cannot condone the practice of seizing upon any opportunity which presents itself to indicate an opinion, either directly or indirectly, that my estimates are insufficient. . . . I shall expect [agency heads] and their subordinates to support only the President's estimates in hearings and discussions with Members of Congress."

--After the hearings, the House and Senate, as in previous years, approved a much higher funding level in FY 1988 than was requested by the Administration.

Current Status of the FY 1988 Budget

- Including funds for AIDS research, which were provided in a separate account under the Office of the Secretary, the House provided a total of $7.0 billion for NIH. This is almost 14 percent above the FY 1987 level and about 18 percent more than the request.

- The Senate provided almost $6.9 billion, 11 percent more than FY 1987 and almost 16 percent above the request.

- As of this time, there has been no House-Senate Conference action to resolve the differences between the House and Senate bills.

- The NIH is currently operating under a Continuing Resolution that provides funding at the FY 1987 operating level of $6.2 billion. This Continuing Resolution will expire on November 10.

- The process that I have just described has played out for many years--with minor variations on the theme, and with slightly varying results--and has become a part of the Washington lore.

- It has also resulted in a history, beginning at least as far back as the early '60s, in which the President's request for the NIH has always been increased by the Congress [SLIDE 4 and SLIDE 5].

This has been true regardless of which Party is in the White House and which Party is in control of the Congress. It is believed by many political pundits that the permissive role played by the Administration in this budgetary theater achieves a final result that conforms to Administration strategy.

The NIH Peer Review System

o The NIH system of peer review has been subjected to constant scrutiny and continues to be a topic of widespread concern. Some of the concerns most frequently voiced are:

oo That it is an "old boys' network";

oo That it favors the Eastern private schools;

oo That it is biased against clinical research;

oo That the administrative burden associated with the process continues to grow at an alarming rate.

o I would like to touch briefly on each of these points.

OLD BOYS' NETWORK

o The claim of an "old boys' network" continues to persist despite the fact that:

  oo We have about 2,000 individuals serving on review bodies in any given year.

  oo Of all DRG study section members serving in 1986, only 15 percent had prior NIH appointments to study sections, compared to 17 percent of those serving in 1975.

  oo Of those members in their first year of appointment in 1986, 17.6 percent had prior NIH experience, compared with 19.0 percent of those first appointed in 1975, and

  oo When the distribution of NIH research funds is compared with the distribution of the organizational affiliations of study section members, it is clear that the great research-intensive universities are, in fact, under-represented on study sections, in proportion to the research dollars they receive.

  oo The average age of study section members is about 45; this has remained fairly constant over the years.

oo Minority representation on chartered study sections has more than doubled since 1976, from 5.7 percent of regular members to 15.0 percent. The distribution of minority membership on study sections reflects roughly the minority representation among NIH grant applicants.

BIAS TOWARD EASTERN PRIVATE SCHOOLS

o The claim that the peer review system favors the Eastern private schools is true to the degree that such schools possess a high concentration of scientific talent sufficient to compete successfully in a system that is, unabashedly, a meritocracy. The Eastern schools, however, have not cornered the market on scientific excellence. In fact, four of the top ten recipients of NIH research grant funds are located on the West Coast. However, the overall pattern of distribution of NIH funds does attest to the concentration of funds in a relatively small number of research-intensive universities across the country. For instance, in FY1986:

oo The top 25 institutions received $1.7 billion, or 38 percent, of NIH extramural awards;

oo The top 100 institutions received about 75 percent of the total dollars for extramural awards;

oo Again, this is a reflection of the philosophy of supporting excellence, without regard to geographical location;

oo Although this distribution pattern has remained relatively constant for many years, recently there has been some modest expansion in the base of institutions receiving NIH support;

--A total of 1,608 institutions received support from NIH in FY1986. This represents an increase of 65 institutions over 1985 and 492 over the number supported 10 years ago.

BIAS AGAINST CLINICAL RESEARCH

o Historically, M.D. investigators, overall, have had less success than their Ph.D. counterparts in competition for NIH research project grants. This fact, however, does not warrant the conclusion that the peer review system is biased against clinical research, in general, or M.D. investigators, in particular.

o The composition of study sections has been cited repeatedly as a cause of this limited success of M.D. grant applicants. However, the proportion of M.D.'s serving on study sections, though declining, remains higher than the proportion of principal investigators on the NIH competing regular research grants (R01) applications that they review [SLIDE 6]. Our latest data indicate

that M.D.'s represented approximately 30 percent of R01 applicants; the percer of study section members holding M.D. degrees was about 35 percent.

oo Of concern to me is the large number of qualified M.D. investigators who have turned down membership on study sections.

o Our studies suggest that factors outside the peer review system are exerting a greater influence on the success rate of M.D. grant applicants. For instance:

oo It is not surprising, in view of the increasing complexity of biomedical research, in general, and the progressive professionalization of clinical research, in particular, that the single most important determinant of the ultimate success of an applicant--M.D. or Ph.D.--in securing NIH research grant support appears to be the length and intensity of research training undertaken in preparation for an investigative career.

o And, it is also not surprising that the physician, even after two or three years of postdoctoral fellowship training, remains less well-trained than the Ph.D. postdoctoral scientist who, in effect, has been training for a research career since the baccalaureate.

o Our analyses show, for instance, that:

oo The longer the postdoctoral training of M.D. investigators, the more likely they are to apply for and receive an NIH research grant. For example,

--in programs in which the median length of training is only 12 months (such programs, incidentally, account for more than one-half of the individuals who enter NIH training programs in clinical settings) only 20 percent of the M.D. trainees ever apply for grants, and about half of them are successful.

--By contrast, about 43 percent of those M.D.'s who receive 30 months or more of research training apply for NIH grants. Well over half of those who apply are successful.

oo As the next two slides indicate, both the application rates and the success rates are much better for M.D.'s who have received training provided under fellowships than for those who received training provided under institutional training grants.

--Ph.D. fellows apply for research grants in the greatest proportions (SLIDE 7], followed by M.D. fellows and Ph.D. trainees. The M.D. trainee shows the poorest application rate.

--Similarly, while Ph.D. fellows enjoy the greatest success rates in obtaining NIH research grants (SLIDE 8], M.D. fellows show the same success rates as Ph.D. trainees.

- Another important NIH program administered by NIGMS is the Medical Scientist Training Program. This program, provides six years of combined clinical and basic science training. It has about 675 individuals in the program at any one time and produces approximately 100 graduates each year. As a result of the research training experience provided through this mechanism, approximately 70 percent of the graduates of this program hold positions in academic medicine. Further analysis of the program is underway.

NIH PEER REVIEW APPEALS SYSTEM

- In 1985 NIH established the peer review appeals process which, in our view, helps to ensure an equitable and complete review of applications for grants and cooperative agreements (assistance awards). By establishing this process, NIH aimed to assure the applicant community that every disputed review will be thoroughly examined and, if significant flaws in substance and/or process are found, appropriate steps will be taken to resolve the matter.

- The appeals process encompasses the entire peer review process of an application from its acceptance and assignment to an initial review group and NIH Institute through its review by the Institute's National Advisory Council.

- The implementation of the appeals process acknowledges the fact that staff and reviewers occasionally make mistakes and that NIH is prepared to give appropriate attention to charges of real or perceived shortcomings in the process or substance of peer review. Capitalizing on the well established practices in the Institutes for handling rebuttal letters, the peer review appeals process consists of a two step system, first, an informal examination of the principal investigator's concerns by the Institute and, second, if necessary, a formal and independent examination through the appeals process, which is located in the Office of Extramural Research.

- Given the extensive examination of the issues in a formal appeal, a delay to the next review cycle of the application should be normally expected. In past history, fewer than 10 formal appeals were submitted annually to NIH. Of these, approximately 40 percent resulted in some corrective action on the part of NIH.

THE PEER REVIEW COMMITTEE

- I have recently appointed a committee under the chairmanship of Dr. Claude Lenfant of National Heart, Lung, and Blood Institute, to identify and assess issues about our peer review process. The committee will also be expected to make recommendations to resolve problems it identifies.

- Although the committee will address issues it considers relevant to its charge, the following questions, representing concerns expressed within the biomedical community, may serve as a guide:

  - Do the study sections assign too much value to the description instead of to the track record of the investigator(s)?

  - Is innovative, creative research given a fair review when it is not supported by preliminary data and particularly when it is proposed by a young investigator?

  - As presently constituted, do the study sections have the necessary expertise to review applications assigned to them?

  - Do study sections view their role as limited to technical merit assessment?

- The committee will also be expected to assess how study section members are selected and the duration of their term.

INCREASING ADMINISTRATIVE BURDEN

- It is no myth that the pressure for greater accountability for the use of Federal funds has: (1) made the grants application process

more burdensome for investigators, university administrators, and members of peer review groups; (2) contributed to additional uncertainty and instability in the careers of extramural scientists; and (3) created impediments to the creativity and productivity of investigators.

o I believe, however, that we have succeeded in making the problem widely recognized and that we have at least begun to turn the corner on some of the most troublesome aspects of this problem.

o One of the factors contributing to the workload of both the grant applicant and the NIH peer review system was the excessive complexity and sheer bulk of the research grant application.

  oo The excessive length of applications resulted largely from a vicious cycle in which study sections tended to engage in excessive scrutiny of applications for minor technical flaws and omissions that, in turn, created the perception among applicants that comprehensive, highly detailed documentation of all aspects of a proposal was required in order to increase the prospects of succeeding in the competition for funds.

  oo We have addressed this problem through the simple ministerial act of shortening and simplifying the research grant application by placing page limitations on such common core

elements as the "experimental design and method" section and the "appendices" section that describes manuscripts and papers accepted for publication.

oo In addition, we have discussed this issue with the members and administrators of peer review groups in an effort to effect those changes in attitudes and behavior necessary to break the cycle of escalating documentation.

o We are also exploring ways of streamlining the post-award phase of the extramural awards process through participation in the so-called Florida Demonstration Project that is designed to peel away some of the regulations and reporting requirements associated with the administration of ongoing research project grants.

oo We will be examining the results of this experiment to determine the effectiveness of these simplification measures and to assess the feasibility and desirability of extending these practices and adopting them as standard NIH policies.

o Previous demands for greater accountability had resulted in a trend toward shorter periods for grant awards. The thought--that originated largely with officials outside of NIH who lacked familiarity with the intrinsic nature of biomedical research--was that shorter awards would permit more frequent opportunities to review scientific progress and, therefore, would improve the overall quality of the research grants being supported by the NIH.

oo As a result of this influence, over time the average length of a research grant award declined.

o The adverse effects of this trend toward shorter periods of award were felt by all grantees since the system created inefficiencies by requiring investigators to expend increasingly larger investments of time and effort in applying at more frequent intervals for ever-shortening periods of support. But the negative implications were expecially profound for new investigators and for well-established scientists at the peak of their creative powers.

oo The shorter award posed a special hardship for first-time research grant recipients since, typically, those individuals had only about 18 months in which to start up a project and accumulate research findings before starting the process of writing a new application for continued research grant support.

--This situation placed first-time grant recipients at a distinct disadvantage in competing for additional research grant support.

oo This trend also created a situation in which established investigators, who have demonstrated outstanding expertise and are widely recognized as leaders in their fields, must continue to compete in the standard manner, at very short intervals, in order to receive continued research grant support.

--This practice was viewed as a wasteful diversion of creative talents.

o In an effort to address these shortcomings, we have recently initiated two new special award mechanisms--the First Independent Research Support and Transition (FIRST) award and the Method to Extend Research in Time (MERIT) award.

oo The FIRST award provides funds for five years to newly independent biomedical investigators to permit them to initiate their own research and demonstrate the merit of their own research ideas. These awards are not renewable; at the end of five years the investigator is expected to submit a traditional research project grant application to continue and extend the research supported by a FIRST award.

oo The MERIT award provides long-term support to investigators whose research competence and productivity are distinctly superior and who are likely to continue to perform in an outstanding manner. The MERIT award affords the principal investigator the chance to receive up to ten years of support in two segments. An initial five-year award is followed by the opportunity to request an extension of three to five additional years through a greatly expedited review of an abbreviated application describing accomplishments during the initial period of the award and stating research plans for the extension period.

--Investigators may not apply for MERIT awards. Following normal initial review of competing research grant applications, National Advisory Councils Boards recommend candidates for MERIT awards and the Institutes confer MERIT status to selected candidates.

o These two new programs join and augment the ranks of such on-going programs as NINCDS's Javits' Awards and NCI's Outstanding Investigator Awards in meeting the special needs of investigators.

o I might add that, through our initial efforts, to simply encourage study sections, advisory councils, and institutes to consider longer awards, the average length of an NIH regular research grant has now increased to approximately 3.8 years, and we look forward to even longer average periods of award [SLIDE 9].

THE NIH INTRAMURAL RESEARCH PROGRAM

o Another view that is expressed from time to time is that the NIH intramural program grows at a rate that outpaces the funding provided for extramural research activities and that the intramural research is conducted without benefit of peer review.

oo Part of this perception grows, undoubtedly, from the same difficulties in following the budget process that I mentioned earlier.

oo Each year the President's budget contains a larger percentage increase for the intramural portion of the research program than for the extramural component. However, the outcome of the complex appropriations process discussed above has been parity of intramural and extramural increases. For example, between 1974 and 1986 the portion of the appropriation for extramural activities grew by 114 percent and that for intramural programs by 111 percent. The fraction of the NIH appropriation spent intramurally tends to drop in years of significant growth. In 1987, only 10.5 percent of the appropriation is being spent intramurally.

oo The intramural programs and scientists are subject to a rigorous peer review that, while different from that accorded grant applications from extramural scientists, is more appropriate to a national laboratory. Each institute has a Board of Scientific Counselors that reviews each intramural program and scientist once every three to four years. Detailed reports are written that contain recommendations concerning levels of support. Scientific directors make periodic adjustments in allocation of space, funds, and positions based on such reviews. Scientists employed by the Clinical Center because of concomitant service roles are included in this system.

oo The scientific directors of NIH meet regularly to review proposals for promotion and for conversion to tenure status. Less than 10 percent of any cohort group of young scientists is eventually offered tenure. Our system is modeled after academic systems, and tenure must be achieved within seven years. We now have 1,116 intramural scientists with permanent appointments, of whom 428 are physician-scientists.

oo I can understand the concerns of those who would like to see the intramural and extramural systems made more alike. To achieve such parity, however, I would prefer to continue my efforts to further reduce the administrative burden associated with the extramural peer review system rather than make more ponderous the peer review process employed in the intramural program.

TRENDS

o Before concluding this discussion of the policies and activities of the NIH, I would like to leave you with an overall impression of some of the major trends that have occurred in the programs of NIH that I believe will serve as an additional backdrop for the discussions that we will be engaging in today.

o The emphasis that NIH places on basic research has been intensified in recent years and continues to be the dominant focus of our activities.

oo In the early 1970s, the fraction of the total NIH budget devoted to basic research was only about 45 percent. By 1980 this figure had reached 52 percent and in 1986 it had grown to 63 percent.

o This trend is further reflected in the prominent position that investigator- initiated research project grants have grown to occupy at NIH.

oo In 1970, NIH funded 10,000 such awards; in 1982 the number was 15,970; by 1986 we had reached 19,300 awards.

oo This increase in numbers of research project grants has been a result both of slow steady budget growth, and of a reduced emphasis upon contracts and, to some extent, on centers. There has also been a decline in the fraction of the budget devoted to training that resulted primarily from the elimination of non-research training following the revision of the Public Health Service Act in 1974.

--The shift of funds among mechanisms during the past 15 years is shown in the next slide [SLIDE 10].

o The average total cost of research project grants (competing and non-competing awards), expressed in constant dollars, has remained

essentially the same over the past 15 years [SLIDE 11]. For instance, the average total cost of $151,847 reached in 1986, when corrected for inflation, is the same as the total average cost found in 1972. However, during this time the indirect cost component for all grant awards has increased from 21 percent to 31.4 percent of the total award, and, accordingly, in constant dollar terms the average direct cost of research project grants has declined 13 percent in the past 15 years.

o Because the increase in the average cost of research grants has become an area of concern, we have compiled some data that may be of interest. In particular, we have focused our attention on the RPG category as a whole and on the R01 specifically as the mechanism of research support that has likely been the most uniform over time. Slide 12 shows the average cost for R01s since 1972. The trends are similar to those for the RPG category of which the R01s are a part.

o Slide 13 shows the relationship of direct to indirect costs for competing R01s. Note the increase percentage attributable to indirect costs. The decline in overall average cost in FY1986 was due to required downward negotiations.

o NIH had been asked to examine more recent changes in average cost for the RPG category and R01s so we focused our attention over the years FY1980-86.

- Slide 14 shows the percent of direct and indirect costs for competing RPGs, again reflecting the higher percentage to indirect costs.

- Slide 15 compares percent changes and reflects the higher percentage change for indirect than direct costs.

- Slide 16 compares the general distribution of budgeted direct costs by category and shows the general pattern is about the same over the years.

- Slide 17 shows the percent change in budgeted direct costs by category for competing R01s.

- Slide 18 shows the percent changes in noncompeting R01 budgeted direct costs.

- Until the mid-1970s, 70 to 75 percent of submitted applications were recommended for funding by study sections, and about one-half of these were funded, for an award rate of 50 percent. The payline (the priority score that includes 90 percent of awards) was typically in the range of 225 to 250.

  - Recently, 90 percent of submitted applications have been recommended for possible funding. The award rate has been 35 to 40 percent and the payline has been about 170 or 180.

- The increase in approved rates undoubtedly reflects an icnrease in the quality of applications. But, it may also reflect changes in study section behavior. Higher priority scores are now given to applications that study sections view favorably. Therefore, paylines are not comparable. In addition, a 38 percent award rate when 90 percent of the applications are recommended for approval (34 percent success rate) is not much different from a 50 percent award rate when 70 percent of the applications are approved (35 percent success rate).

ISSUES

- In 1970 NIH received 7,570 new and competing renewal applications for R01 and P01 awards. By 1980 this number had reached 13,591, and in 1986 it was 15,858. In 1970 five percent of these were amended applications, or "resubmissions"; in 1980 this figure was 15 percent and in 1986 it was 28 percent of the total. In addition, as competition has increased, more scientists are submitting multiple applications in the hope that at least one will be funded. The component has increased from 10 percent of applicants in 1970 to 17 percent in 1986.

- On balance, these statistics are not cause for gloom or despair. There are, however, mounting challenges to the research system that must be met if we are to maintain the health of the enterprise.

oo The best hope for significant progress in basic research continues to be through the efforts of individual investigators pursuing their own ideas in response to the dictates of the internal logic of science and not in response to the demands of narrow categorical objectives.

oo In this regard, it is essential to provide a steady and predictable level of funding for basic research through the support of investigator-initiated research project grants awarded on the basis of national competition and judged by panels of peers drawn from the ranks of non-Federal research organizations.

o We must address the issue of the role of "big science" in biology by devising appropriate ways to achieve a balance between the need which exists to maintain an adequate level of support for free-ranging, investigator- initiated research and the needs which arise to mount major initiatives in response to emerging opportunities that, by their intrinsic nature, call for large-scale, highly organized, and centrally directed activities requiring sophisticated equipment, extensive information processing, and the sharing of large, specialized facilities.

o Support for research training must be provided at levels sufficient to assure a continuous supply of scientists trained in areas appropriate to meet our national research needs.

- We cannot afford to continue to ignore the declining health of the research institutions in which the bulk of basic research in this country is conducted.

  - A concerted effort must be made to address the growing need to find appropriate ways to strengthen and maintain the research infrastructure by overcoming shortages and obsolescence of research instrumentation and correcting for the physical deterioration of laboratories, animal buildings, and other research facilities.

- Simplification must be achieved in the Federal system of sponsored research to reduce the administrative burden associated with the conduct and management of research to the absolute minimum consistent with the appropriate stewardship of public funds.

- Every effort must be made to restore and maintain public confidence in the support of research by promoting the highest personal standards of integrity among scientists and assuring the proper care and use of animals used in research.

  - There is also a critical need to develop a better understanding among the mass media, elected officials, and the general public of the scientific imperative of using animals in research.

oo The current attacks on biological research must be taken seriously and responded to with scientific fact and evidence of the strength of our commitment to the pursuit of important goals through responsible use of animals in research.

CONCLUSION

o I hope that my remarks today have served to describe the broad context in which the NIH operates, to dispel some of the popular misconceptions concerning NIH budgets and programs by demonstrating the salient features of recent trends in NIH activities, to share with you the broad goals and strategies that condition and influence current and emerging NIH policies and practices, and to encourage you to develop and maintain a keen awareness of the process by which science budgets are developed and increase your active participation in that process.

o In my discussion, I have alluded to only a few of the host of pressing issues that exist concerning the impact of the Federal system of sponsored research on the health of biomedical research institutions. Many of these problems have emerged as a result of the increasing complexity of the research environment engendered by unprecedented scientific ferment and growing public awareness of the process and social impact of science. Others have long existed in a chronic state and now threaten to assume crisis proportions. It is to such issues that the remainder of this meeting is to be addressed.

- At this point, I would be pleased to answer any questions you might have and to respond to any comments you may wish to make.

- If there are no futher questions or comments, I will proceed to the presentations of our public witnesses.

- As you can see, we have not provided a highly-structured agenda for the public forum portion of this meeting; instead, we would like to encourage a free-ranging discussion that will help us to identify those issues which you, the members of the scientific and academic community, perceive to be of greatest import and to solicit your views on solutions to these problems and your suggestions for future directions.

REMARKS*

by

James B. Wyngaarden, M.D.**

On behalf of the National Institutes of Health it is my pleasure and honor to express our deepest gratitude to all our Canadian friends for this memorable day. Your thoughtfulness in celebrating the 100th birthday of the NIH is typical of the closensss and warmth of the relationship that has existed between the scientific communities of the United States and Canada. More specifically, it is an extension of the ties that have developed in the course of our common scientific endeavor against disease and disability.

The centennial year has been an exhilarating experience for all of us who are a part of the NIH. In addition to several events at our headquarters in Bethesda, and a special observance at the site of our founding on Staten Island in New York, there have been a score or more of regional dinners and symposia at major centers of medical research throughout the United States. Alumni of our intramural visitors programs and former staff members have held centennial celebrations overseas. The Medical Research Council of New Zealand, the European Medical Research Council, and the British Medical Research Councils have dedicated scientific conferences to the NIH's role in medical progress over the past century.

There is a neighborly quality about this occasion, however, that sets it apart. Nearly 30 Canadian academic institutions, hospitals and other laboratories participate with us in our extramural programs, and these organizations administer about 180 active grants and contracts. Except for institutions within the United States, Canadian grantees and contractors receive by far the largest amount of awards from the NIH. We are also pleased that there are 65 Canadians now in Bethesda, working with our

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*Presented at the Canadian MRC program in honor of the NIH Centennial in Montreal, Canada, November 12, 1987.

**Director, National Institutes of Health, Bethesda, Maryland

intramural scientists as participants in our visiting programs for talented scientists from throughout the world.

At the time the first modest steps were taken toward establishment of the National Institutes of Health, it is unlikely that much thought was given to the international collaboration that ultimately would become a significant part of our programs. Such exchanges have brought new insights and inspiration, and we believe have been of great benefit to both partners and to the world.

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease is of preeminent concern, and national policy concerning biomedical research is of surpassing concern in all countries. Its significance is truly universal, for as Disraeli said, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."[1]

REFERENCE

[1]Disraeli, The Shorter Bartletts Familiar Quotations, Doubleday and Co., Garden City, New York, 1952, p. 106.

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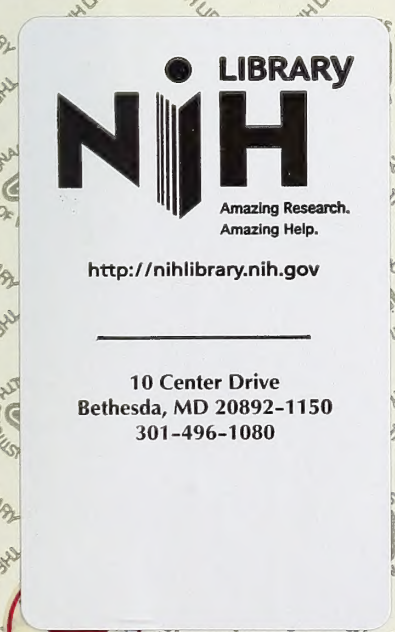
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